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46TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE

ACID-BASE PHYSIOLOGY AND DISORDERS

- Foreword: Acid-Base Disturbance
- Acid-Base Physiology
- Metabolic Acidosis
- Metabolic Alkalosis
- Respiratory Acidosis
- Respiratory Alkalosis
- Approach to Patients with Acid-Base Disorders

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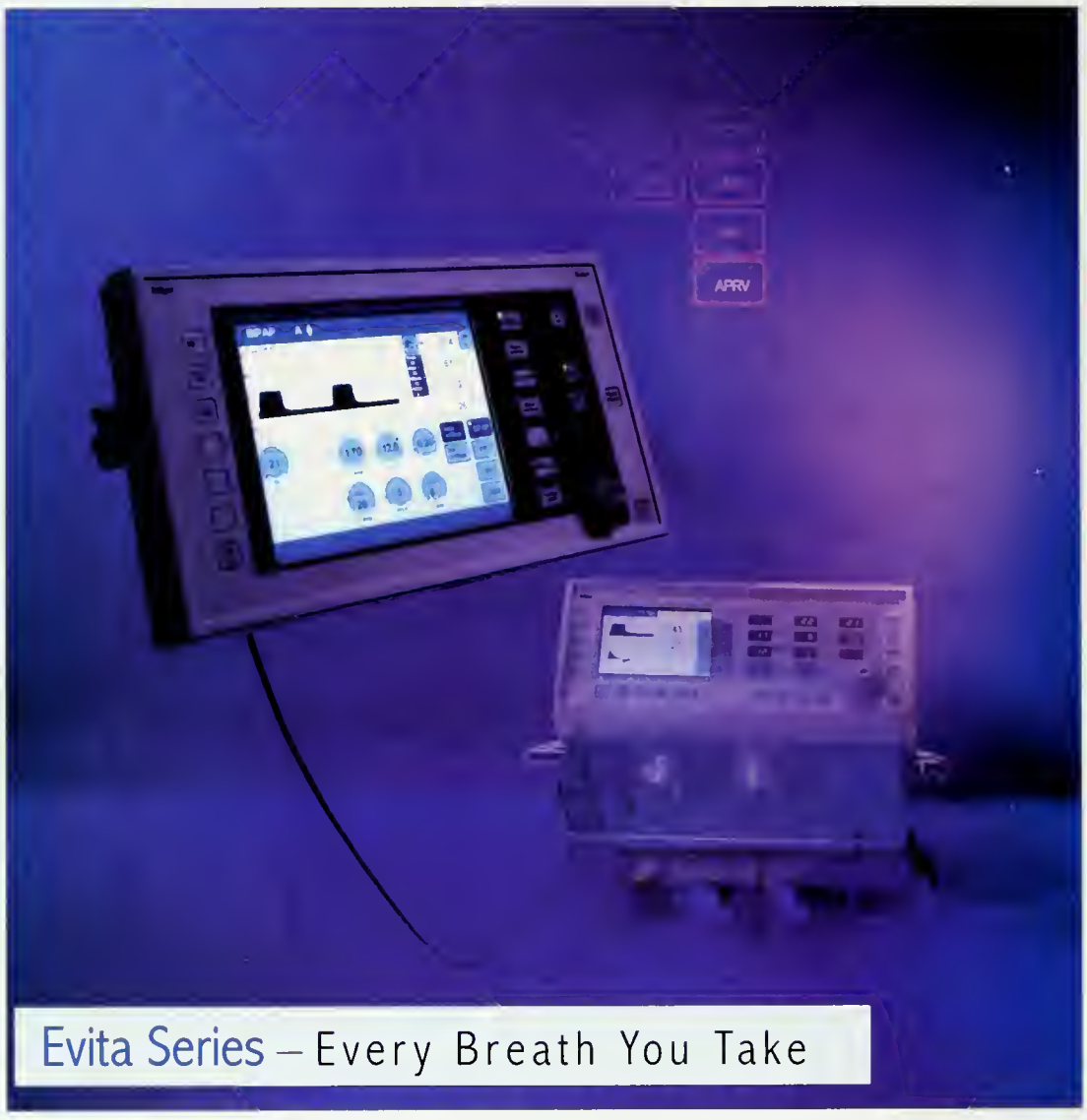

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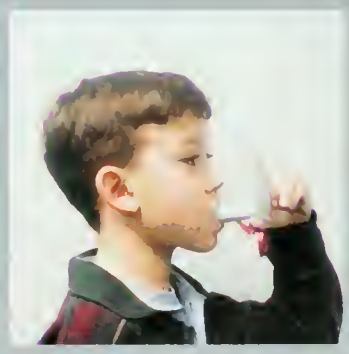

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ACID-BASE PHYSIOLOGY AND DISORDERS

A SPECIAL ISSUE

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Editorials, Commentaries, and Reviews To Note

Primary Care: The Diagnosis and Treatment of Cough (review)—Irwin RS, Madison JM. N Engl J Med 2000 Dec 7;343(23):1715-1721.

Percutaneous Dilatational Vs Standard Tracheotomy: A Meta-Analysis but Not the Final Analysis—Heffner JE. Chest 2000 Nov;118(5):1236-1238.

Withdrawing Life Support from the Critically Ill—McGee DC, Weinacker AB, Raffin TA. Chest 2000 Nov;118(5):1238-1239.

Managed Care of Chronically Ill Older People: The US Experience—Boult C, Kane RL, Brown R. BMJ 2000 Oct 21;321(7267):1011-1014

Is There More to Lung Development than Steroids and Surfactant?—Rajagopal J, Kinane TB. Pediatrics 2000 Nov;106(5):1103-1104.

Respiratory Mechanics in ARDS: A Siren for Physicians?—Pelosi P, Gattinoni L. Intensive Care Med 2000 Jun;26(6):653-656.

Organization of Personnel and Resources for Airway Management in the Hospital and Office Environment—Showan AM, Sestito JA. Crit Care Clin 2000 Jul;16(3):527-539.

Good airway management depends on a system that emphasizes teamwork to expedite care and minimize errors. By understanding the accreditation and licensing requirements, appropriate personnel and equipment can be allocated along cost effective guidelines. Newer techniques for management of the difficult airway, such as the laryngeal mask airway (LMA; LMA North America, San Diego, CA) and flexible fiberoptic bronchoscope, provide alternatives to the emergency cricothyrotomy. A program of continuous quality improvement and clinical guidelines will enhance patient care and suggest intelligent use of airway resources.

The Role of Fiberoptic Bronchoscopy in Airway Management of the Critically Ill Patient—Weiss YG, Deutschman CS. Crit Care Clin 2000 Jul;16(3):445-451.

Fiberoptic bronchoscopes (FOB) play a pivotal role in airway management in the operating room and critical care environments. This article examines the role of FOBs in modern airway management based on a review of recent literature and personal experience.

Augmented Fiberoptic Intubation—Barnett RA, Ochroch EA. Crit Care Clin 2000 Jul;16(3):453-462.

Patients who are difficult to intubate are randomly encountered. Patients who are in the postoperative period or who have suffered trauma have a greater chance of being difficult to intubate. The ability to quickly mobilize trained personnel and advanced equipment provides the best chance for a good outcome for these patients. Practice in placement of and intubation with LMAs is an important step toward providing an extensive safety net for patients needing intubation.

Airway Management in the Obstetric Patient—Lewin SB, Cheek TG, Deutschman CS. Crit Care Clin 2000 Jul;16(3):505-513.

In summary, the need to manipulate the airway in the pregnant patient requires careful consideration and substantial planning. Anatomic and physiologic changes of pregnancy, coexisting conditions, and the potential for aspiration all carry a risk of morbidity and, indeed, mortality. Preparation, including early and repeated airway evaluations throughout pregnancy and labor, is encouraged. Knowledge of an emergency airway algorithm and a well thought-out plan for difficult intubations are imperative. Equipment must be available and in good condition. Finally, proper education and review for individuals involved in the delivery of care on the labor floor are mandatory. Although it is not always possible to control the manner in which these patients present, it is usually possible to control the environment into which they present.

Teaching Airway Management Skills: How and What to Learn and Teach—Gaiser RR. Crit Care Clin 2000 Jul;16(3):515-525.

It is important to instruct all individuals involved in patient care in airway management. The degree of skills actually taught depends on the student. Currently, there are many options for teaching. Mannequin training is the one best suited to instruct a large number of students in a variety of skills. Training of surgical and obstetric residents improves relations, may improve patient safety, and educates these individuals regarding the risks of failed intubation. Actual clinical decisions regarding patient management are based on the airway examination. There is room for improvement in instruction, even in anesthesiology programs. Various techniques must be taught and practiced. As more anesthesiologists become trained and then train other physicians, the number of cases in the Closed Claims Study involving the airway will continue to decrease.

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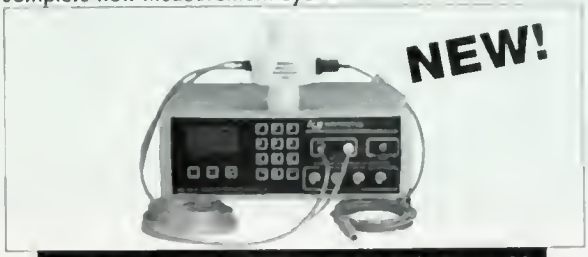

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Bridges to Establish an Emergency Airway and Alternate Intubating Techniques—Foley LJ, Ochroch EA. Crit Care Clin 2000 Jul;16(3):429-444.

In this article, a number of alternatives to direct laryngoscopy are examined. These alternatives include the laryngeal mask airway (LMA; LMA North America, San Diego, CA), cuffed oropharyngeal airway (COPA; Mallinckrodt, St. Louis, MO), and Combitube (Kendall-Sheridan, Mansfield, MA), that have been designed to act as bridges to establish an airway. Other devices, such as rigid stylets, the lightwand (a blind technique) and indirect fiberoptic rigid stylets, such as the Bullard scope, Upsher scope, and Wu scope are also briefly discussed.

Pediatric Airway Issues—Levy RJ, Helfaer MA. Crit Care Clin 2000 Jul;16(3):489-504.

Airway management in the pediatric patient requires an understanding and knowledge of the differences and characteristics unique to the child and infant. New and exciting techniques are currently being explored and developed for management of the pediatric airway. Technology in the area of imaging has allowed clinicians to better visualize the airway and aberrations of it. Presently, there are many different modes and routes of ventilation and oxygenation that are being applied to the pediatric patient for different disease states. Work continues to probe for methods and ways that will allow us to take care of infants and children better and to provide the safest and most effective means of delivering that care. No doubt, there will be more advances and exciting ideas to come that lead to better management of the pediatric airway.

Surgical Airway Management in the Intensive Care Unit—Pryor JP, Reilly PM, Shapiro MB. Crit Care Clin 2000 Jul;16(3):473-488.

Despite having been a known surgical procedure for over 5000 years, the specifics of how, when, and why to perform a surgical airway are still debated. With new procedures, equipment, and techniques, operative airway management is becoming more complex. New methods of surgical airway management have to be evaluated against the gold standard, which will always be the open tracheostomy performed in the operating room. Unlike Dr. Jackson in 1909, surgeons today have to evaluate these new procedures not only by their efficacy but also by their cost effectiveness.

Transtracheal Oxygen Delivery—Eckmann DM. Crit Care Clin 2000 Jul;16(3):463-472.

Tracheal insufflation of oxygen has at least three major uses for chronic oxygen supplementation through a percutaneous catheter, it is an adjunctive measure to enhance gas exchange during mechanical ventilation, and it provides an emergency therapy for oxygen delivery with upper airway obstruction. In this article the mechanisms of gas exchange and techniques of oxygen delivery are described for each of these major uses.

Emergent Airway Management: Indications and Methods in the Face of Confounding Conditions—Rodricks MB, Deutschman CS. Crit Care Clin 2000 Jul;16(3):389-409.

Optimal airway management requires an experienced caregiver, attention to detail, and knowledge of the patient's physiology. A variety of pharmacologic agents have proved useful in obtaining a secure airway and minimizing risk to the patient. Depending on the skills of the caregiver, oral intubation has become the preferred means of airway control in most patients. Advances in technique, equipment, and pharmacology have greatly improved the art of airway management; however, there is no substitute for an experienced clinician.

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PROGRAM GUIDE

PROGRAM #1

Taking the Mystery Out of Weaning the Pediatric Patient from the Ventilator

Peter Betit, BS, RRT, FAARC, and Richard D. Branson, BA, RRT, FAARC

Learn when to begin the process and how to recognize critical events in weaning a pediatric patient. Also teaches the physiological differences between the adult and pediatric patient and why weaning of the pediatric patient is different. The presentation confronts participants with options in providing assisted ventilation and the correct selection of options that expedite weaning.

Live Videoconference -
March 13, 11:30 a.m. - 1:00 p.m. Central Time
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April 10, 11:30 a.m. - 12:00 Noon Central Time

PROGRAM #2

Pulmonary Rehabilitation: Standard Care for Chronic Lung Disease Patients

Trina Limberg, BS, RRT, and Thomas J. Kallstrom, RRT, FAARC

Presentation details when to refer a patient for pulmonary rehabilitation and the four elements necessary for the successful operation of a rehabilitation service. Details how to prepare a treatment plan during assessment and how to modify it based on subsequent evaluations as well as how to incorporate rehabilitation techniques into routine bedside therapy sessions.

Live Videoconference -
March 27,11:30 a.m. - 1:00 p.m. Central Time
Teleconference with Videotape -
April 17, 11:30 a.m. - 12:00 Noon Central Time

PROGRAM #3

Noninvasive Ventilation: The Latest Word

Dean R. Hess, PhD, RRT, FAARC, and Richard D. Branson, BA, RRT, FAARC

Learn how to avoid intubation in the acutely ill patient through identification of patients most likely to benefit from noninvasive ventilation. Learn selection and proper fit of full masks or nasal masks and how to select the proper ventilator based on the patient's condition and desired outcomes. Also learn when to make adjustments to achieve the goals of unloading respiratory muscles and achieving good patient/ventilator synchrony.

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April 24, 11:30 a.m. - 1:00 p.m. Central Time
Teleconference with Videotape -
May 29, 11:30 a.m. - 12:00 Noon Central Time

PROGRAM #4

Education of the Patient with Asthma

Tracey Mitchell, RRT, RPFT, and Thomas J. Kallstrom, RRT, FAARC

This program teaches how to ensure that patients understand the disease process of asthma and their care plan for effective disease management. And, it details what patient education materials are available, their content, where to find them, and the best methods of presentation, including new terminologies, analogies, and techniques.

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May 22, 11:30 a.m. - 1:00 p.m. Central Time
Teleconference with Videotape -
June 19, 11:30 a.m. - 12:00 Noon Central Time

PROGRAM #5

ARDS: The Disease and Its Management

Leonard D. Hudson, MD, and David J. Pierson, MD, FAARC

Presents the four diagnostic criteria for ARDS and the six clinical risk factors that place patients at increased likelihood for developing ARDS. The program will teach viewers how to understand the implications of the lower and upper inflection points on the pressure-volume curve of the respiratory system in ARDS patients; and instruct them in the calculation of estimated required tidal volume.

Live Videoconference -
June 26, 11:30 a.m. - 1:00 p.m. Central Time
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PROGRAM #6

New Respiratory Drugs: What, When, and How?

Joseph L. Rau, PhD, RRT, FAARC, and Patrick J. Dunne, MEd, RRT, FAARC

Introduces participants to new formulations such as racemic drug mixtures and single isomers and their effective duration and how they lead to lower costs with improved patient responses. Viewers will learn the use of improved anticholinergics in the treatment of asthma patients and learn the uses and effects of inhaled anti-infective agents.

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PROGRAM #7

Invasive Ventilation: The Latest Word

Richard Kallet, MS, RRT and Richard D. Branson, BA, RRT FAARC

Learn how proper ventilator management can preclude inflicting harm on the patient and why it is essential for the clinician to understand the function and mechanics of newer mechanical ventilators. Also learn how reducing the patient's work of breathing is essential in reducing the additional load on ventilatory musculature, and why reinflating lungs and enhancing the functional area of the lung demands extraordinary means.

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Sept. 25, 11:30 a.m. - 1:00 p.m. Central Time
Teleconference with Videotape -
Oct. 16, 11:30 a.m. - 12:00 Noon Central Time

PROGRAM #8

Test Your Lungs, Know Your Numbers, Prevent Emphysema

Thomas L. Petty, MD, FAARC and David J. Pierson, MD, FAARC

Reviews the classic signs of COPD with an emphasis on emphysema and a discussion on the measures used to relieve symptoms and slow disease progression. Covers the importance of pulmonary function tests to determine VC, FFC, and FEV_1; and why getting patients to know their numbers is the key to early diagnosis and successful treatment.

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Operation Everest III: Role of Plasma Volume Expansion on $\dot{V}O_{2max}$ during Prolonged High-Altitude Exposure—Robach P, Dechaux M, Jarrot S, Vaysse J, Schneider JC, Mason NP, et al. J Appl Physiol 2000 Jul;89(1):29-37.

We hypothesize that plasma volume decrease (ΔPV) induced by high-altitude (HA) exposure and intense exercise is involved in the limitation of maximal O_2 uptake ($\dot{V}O_{2max}$) at HA. Eight male subjects were decompressed for 31 days in a hypobaric chamber to the barometric equivalent of Mt. Everest (8,848 m). Maximal exercise was performed with and without plasma volume expansion (PVX, 219-292 mL) during exercise, at sea level (SL), at HA (370 mm Hg, equivalent to 6, 000 m after 10-12 days) and after return to SL (RSL, 1-3 days). Plasma volume (PV) was determined at rest at SL, HA, and RSL by Evans blue dilution. PV was decreased by 26% ($p < 0.01$) at HA and was 10% higher at RSL than at SL. Exercise-induced ΔPV was reduced both by PVX and HA ($p < 0.05$). Compared with SL, $\dot{V}O_{2max}$ was decreased by 58 and 11% at HA and RSL, respectively. $\dot{V}O_{2max}$ was enhanced by PVX at HA (+9%, $p < 0.05$) but not at SL or RSL. The more PV was decreased at HA, the more $\dot{V}O_{2max}$ was improved by PVX ($p < 0.05$). At exhaustion, plasma renin and aldosterone were not modified at HA compared with SL but were higher at RSL, whereas plasma atrial natriuretic factor was lower at HA. The present results suggest that PV contributes to the limitation of $\dot{V}O_{2max}$ during acclimatization to HA. RSL-induced PVX, which may be due to increased activity of the renin-aldosterone system, could also influence the recovery of $\dot{V}O_{2max}$.

Sustained Isocapnic Hypoxia Suppresses the Perception of the Magnitude of Inspiratory Resistive Loads—Orr RS, Jordan AS, Catcheside P, Saunders NA, McEvoy RD. J Appl Physiol 2000 Jul;89(1):47-55.

The sensation of increased respiratory resistance or effort is likely to be important for the initiation of alerting or arousal responses, particularly in sleep. Hypoxia, through its central nervous system-depressant effects, may decrease the perceived magnitude of respiratory loads. To examine this, we measured the effect of isocapnic hypoxia on the ability of 10 normal, awake males (mean age = 24.0 ± 1.8 yr) to magnitude-scale five externally applied inspiratory resistive loads (mean values from 7.5 to 54.4 cm $H_2O \cdot L^{-1} \cdot s$). Each subject scaled the loads during 37 min of isocapnic hypoxia (inspired O_2 fraction = 0.09, arterial O_2 saturation of 80%) and during 37 min of normoxia, using the method of open magnitude numerical scaling. Results were normalized by modulus equalization to allow between-subject comparisons. With the use of peak inspiratory pressure (PIP) as the measure of load stimulus magnitude, the perception of load magnitude (ψ) increased linearly with load and, averaged for all loaded breaths, was significantly lower during hypoxia than during normoxia (20.1 ± 0.9 and 23.9 ± 1.3 arbitrary units, respectively; $p = 0.048$). ψ declined with time during hypoxia ($p = 0.007$) but not during normoxia ($p = 0.361$). Our result is remarkable because PIP was higher at all times during hypoxia than during normoxia, and previous studies have shown that an elevation in PIP results in increased ψ. We conclude that sustained isocapnic hypoxia causes a progressive suppression of the perception of the magnitude of inspiratory resistive loads in normal subjects and could, therefore, impair alerting or arousal responses to respiratory loading.

Effect of the Mechanical Ventilatory Cycle on Thermodilution Right Ventricular Volumes and Cardiac Output—Groeneveld AB, Berendsen RR, Schneider AJ, Pneumatikos IA, Stokkel LA, Thijs LG. J Appl Physiol 2000 Jul;89(1):89-96.

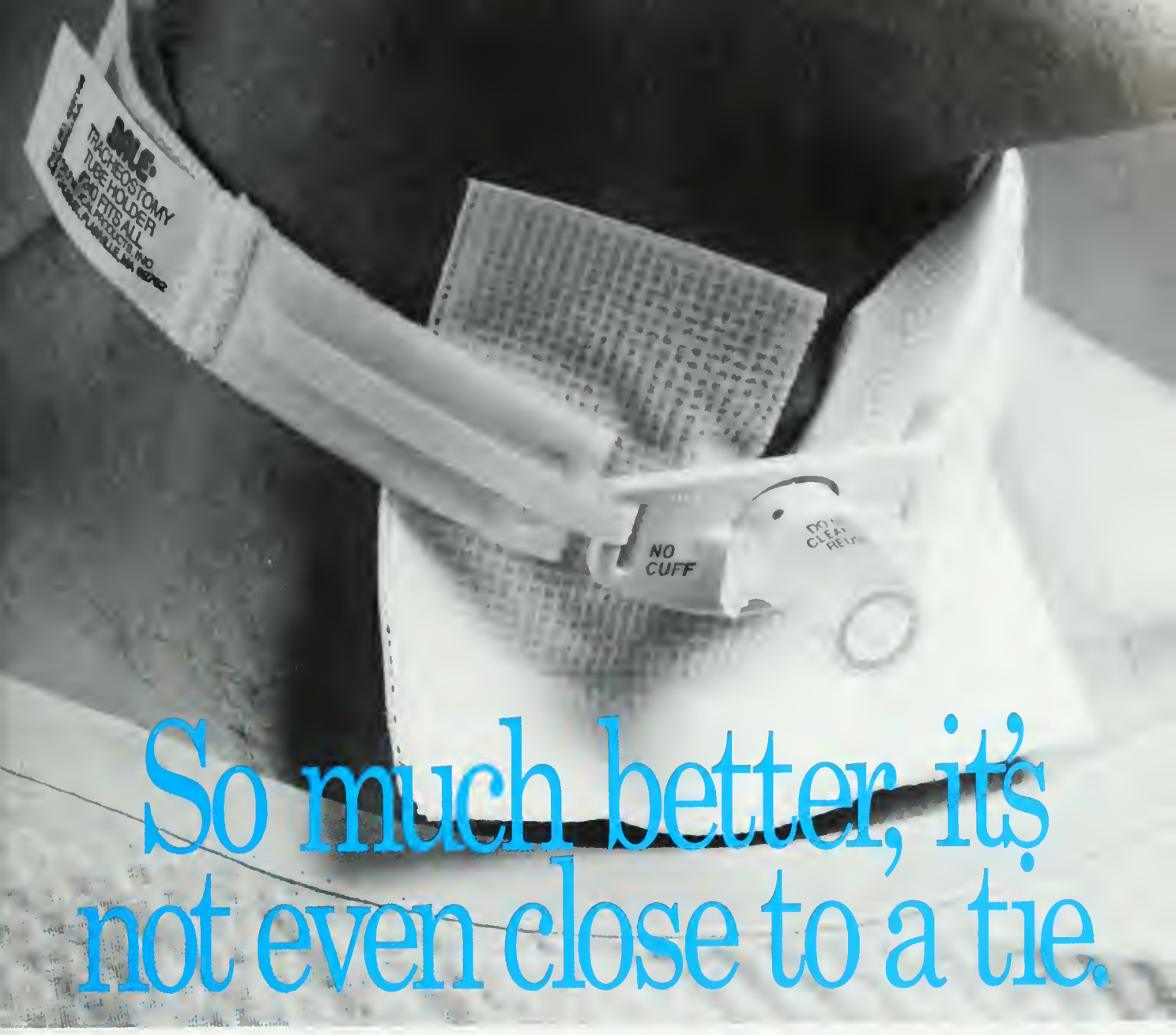
The purpose of this study was to evaluate right ventricular (RV) loading and cardiac output changes, by using the thermodilution technique, during the mechanical ventilatory cycle. Fifteen critically ill patients on mechanical ventilation, with 5 cm H_2O of positive end-expiratory pressure, mean respiratory frequency of 18 breaths/min, and mean tidal volume of 708 mL, were studied with help of a rapid-response thermistor RV ejection fraction pulmonary artery catheter, allowing 5-mL room-temperature 5% isotonic dextrose thermodilution measurements of cardiac index (CI), stroke volume (SV) index, RV ejection fraction (RVEF), RV end-diastolic volume (RVEDV), and RV end-systolic volume (RVESV) indexes at 10% intervals of the mechanical ventilatory cycle. The ventilatory modulation of CI and RV volumes varied from patient to patient, and the interindividual variability was greater for the latter variables. Within patients also, RV volumes were modulated more by the ventilatory cycle than CI and SV index. Around a mean value of 3.95 ± 1.18 $L \cdot min^{-1} \cdot m^{-2}$ (= 100%), CI varied from 87.3 ± 5.2 (minimum) to 114.3 ± 5.1% (maximum), and RVESV index varied between 61.5 ± 17.8 and 149.3 ± 34.1% of mean 55.1 ± 17.9 mL/m^2 during the ventilatory cycle. The variations in the cycle exceeded the measurement error even though the latter was greater for RVEF and volumes than for CI and SV index. For mean values, there was an inspiratory decrease in RVEF and increase in RVESV, whereas a rise in RVEDV largely prevented a fall in SV index. We conclude that cyclic RV afterloading necessitates multiple thermodilution measurements equally spaced in the ventilatory cycle for reliable assessment of RV performance during mechanical ventilation of patients.

Characterization of Pharyngeal Resistance during Sleep in a Spectrum of Sleep-Disordered Breathing—Tamisier R, Pepin JL, Wuyam B, Smith R, Argod J, Levy P. J Appl Physiol 2000 Jul;89(1):120-130.

Aims of the study were 1) to compare Hudgel's hyperbolic with Rohrer's polynomial model in describing the pressure-flow relationship, 2) to use this pressure-flow relationship to describe these resistances and to evaluate the effects of sleep stages on pharyngeal resistances, and 3) to compare these resistances to the pressure-to-flow ratio ($\Delta P/V$). We studied 12 patients: three with upper airway resistance syndrome (UARS), four with obstructive sleep hypopnea syndrome (OSHS), three with obstructive sleep apnea syndrome (OSAS), and two with simple snoring (SS). Transpharyngeal pressures were calculated between choanae and epiglottis. Flow was measured by use of a pneumotachometer. The pressure-flow relationship was established by using nonlinear regression and was appreciated by the Pearson's square (r^2). Mean resistance at peak pressure (R_{max}) was calculated according to the hyperbolic model during stable respiration. In 78% of the cases, the value of r^2 was greater when the hyperbolic model was used. We demonstrated that R_{max} was in excellent agreement with P/V. UARS patients exhibited higher awake mean R_{max} than normal subjects and other subgroups and a larger increase from wakefulness to slow-wave sleep than subjects with OSAS, OSHS, and SS. Analysis of breath-by-breath changes in R_{max} was also a sensitive method to detect episodes of high resistance during sleep.

Effects of Respiratory Muscle Work on Exercise Performance—Harms CA, Wetter TJ, St Croix CM, Pegelow DF, Dempsey JA. J Appl Physiol 2000 Jul;89(1):131-138.

The normal respiratory muscle effort at maximal exercise requires a significant fraction of cardiac output and causes leg blood flow to fall. We questioned whether the high levels of respiratory muscle work experienced in heavy exercise would affect performance. Seven male cyclists [maximal O_2 consumption ($\dot{V}_{O_2}$) 63 ± 5 $mL \cdot kg^{-1} \cdot min^{-1}$] each completed 11 randomized trials on a cycle ergometer at a workload requiring 90% maximal $\dot{V}_{O_2}$. Respiratory muscle work was either decreased (unloading), increased (loading), or unchanged (control). Time to exhaustion was increased with unloading in 76% of the trials by an average of 1.3 ± 0.4 min or 14 ± 5% and decreased with loading in 83% of the trials by an average of 1.0 ± 0.6 min or 15 ± 3% compared with control ($p < 0.05$). Respiratory muscle unloading during exercise reduced $\dot{V}_{O_2}$, caused hyperventilation, and reduced the rate of change in



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perceptions of respiratory and limb discomfort throughout the duration of exercise. These findings demonstrate that the work of breathing normally incurred during sustained, heavy-intensity exercise (90% V_{O_2}) has a significant influence on exercise performance. We speculate that this effect of the normal respiratory muscle load on performance in trained male cyclists is due to the associated reduction in leg blood flow, which enhances both the onset of leg fatigue and the intensity with which both leg and respiratory muscle efforts are perceived.

Effect of Gender on the Development of Hypocapnic Apnea/Hypopnea During NREM Sleep—Zhou XS, Shahabuddin S, Zahn BR, Babcock MA, Badr MS. J Appl Physiol 2000 Jul;89(1):192-199.

We hypothesized that a decreased susceptibility to the development of hypocapnic central apnea during non-rapid eye movement (NREM) sleep in women compared with men could be an explanation for the gender difference in the sleep apnea/hypopnea syndrome. We studied eight men (age 25-35 yr) and eight women in the midluteal phase of the menstrual cycle (age 21-43 yr); we repeated studies in six women during the midfollicular phase. Hypocapnia was induced via nasal mechanical ventilation for 3 min, with respiratory frequency matched to eupneic frequency. Tidal volume (V_T) was increased between 110 and 200% of eupneic control. Cessation of mechanical ventilation resulted in hypocapnic central apnea or hypopnea, depending on the magnitude of hypocapnia. Nadir minute ventilation in the recovery period was plotted against the change in end-tidal P_{CO_2} (P_{ETCO_2}) per trial; minute ventilation was given a value of 0 during central apnea. The apneic threshold was defined as the x-intercept of the linear regression line. In women, induction of a central apnea required an increase in V_T to 155 ± 29% (mean ± SD) and a reduction of P_{ETCO_2} by -4.72 ± 0.57 torr. In men, induction of a central apnea required an increase in V_T to 142 ± 13% and a reduction of P_{ETCO_2} by -3.54 ± 0.31 torr ($p = 0.002$). There was no difference in the apneic threshold between the follicular and the luteal phase in women. Premenopausal women are less susceptible to hypocapnic disfacilitation during NREM sleep than men. This effect was not explained by progesterone. Preservation of ventilatory motor output during hypocapnia may explain the gender difference in sleep apnea.

Peak Flowmeter Resistance Decreases Peak Expiratory Flow in Subjects with COPD—Miller MR, Pedersen OF. J Appl Physiol 2000 Jul; 89(1):283-290.

Previous studies have shown that the added resistance of a mini-Wright peak expiratory flow (PEF) meter reduced PEF by approximately 8% in normal subjects because of gas compression reducing thoracic gas volume at PEF and thus driving elastic recoil pressure. We undertook a body plethysmographic study in 15 patients with chronic obstructive pulmonary disease (COPD), age 65.9 ± 6.3 yr (mean ± SD, range 53-75 yr), to examine whether their recorded PEF was also limited by the added resistance of a PEF meter. The PEF meter increased alveolar pressure at PEF (P_{peak}) from 3.7 ± 1.4 to 4.7 ± 1.5 kPa ($p = 0.01$), and PEF was reduced from 3.6 ± 1.3 L/s to 3.2 ± 0.9 L/s ($p = 0.01$). The influence of flow limitation on PEF and P_{peak} was evaluated by a simple four-parameter model based on the wave-speed concept. We conclude that added external resistance in patients with COPD reduced PEF by the same mechanisms as in healthy subjects. Furthermore, the much lower P_{peak} in COPD patients is a consequence of more severe flow limitation than in healthy subjects and not of deficient muscle strength.

Detecting Lung Overdistention in Newborns Treated with High-Frequency Oscillatory Ventilation—Weber K, Courtney SE, Pyon KH, Chang GY, Pandit PB, Habib RH. J Appl Physiol 2000 Jul;89(1):364-372.

Positive airway pressure (P_{aw}) during high-frequency oscillatory ventilation (HFOV) increases lung volume and can lead to lung overdistention with potentially serious adverse effects. To date, no method is available to monitor changes in lung volume (ΔVL) in HFOV-treated infants to avoid overdistention. In five newborn piglets (6-15 days old, 2.2-4.2 kg), we investigated the use of direct current-coupled respiratory inductive plethysmography (RIP) for this purpose by evaluating it against whole body plethysmography. Animals were instrumented, fitted with RIP bands, paralyzed, sedated, and placed in the plethysmograph. RIP and plethysmography were simultaneously calibrated, and HFOV was instituted at varying P_{aw} settings before (6-14 cm H_2O) and after (10-24 cm H_2O) repeated warm saline lung lavage to induce experimental surfactant deficiency. Estimates of ΔVL from both methods were in good agreement, both transiently and in the steady state. Maximal changes in lung volume (ΔVL_{max}) from all piglets were highly correlated with ΔVL measured by RIP (in mL) = 1.01 × changes measured by whole body plethysmography - 0.35; $r^2 = 0.95$. Accuracy of RIP was unchanged after lavage. Effective respiratory system compliance (C_{eff}) decreased after lavage, yet it exhibited similar sigmoidal dependence on ΔVL_{max} pre- and post-lavage. A decrease in C_{eff} (relative to the previous P_{aw} setting) as ΔVL_{max} was methodically increased from low to high P_{aw} provided a quantitative method for detecting lung overdistention. We conclude that RIP offers a noninvasive and clinically applicable method for accurately estimating lung recruitment during HFOV. Consequently, RIP allows the detection of lung overdistention and selection of optimal HFOV from derived C_{eff} data.

Physiology in Microgravity—West JB. J Appl Physiol 2000 Jul;89(1): 379-384.

Studies of physiology in microgravity are remarkably recent, with almost all the data being obtained in the past 40 years. The first human spaceflight did not take place until 1961. Physiological measurements in connection with the early flights were crude, but, in the past 10 years, an enormous amount of new information has been obtained from experiments on Spacelab. The United States and Soviet/Russian programs have pursued different routes. The US has mainly concentrated on relatively short flights but with highly sophisticated equipment such as is available in Spacelab. In contrast, the Soviet/Russian program concentrated on first the Salyut and then the Mir space stations. These had the advantage of providing information about long-term exposure to microgravity, but the degree of sophistication of the measurements in space was less. It is hoped that the International Space Station will combine the best of both approaches. The most important physiological changes caused by microgravity include bone demineralization, skeletal muscle atrophy, vestibular problems causing space motion sickness, cardiovascular problems resulting in postflight orthostatic intolerance, and reductions in plasma volume and red cell mass. Pulmonary function is greatly altered but apparently not seriously impaired. Space exploration is a new frontier with long-term missions to the moon and Mars not far away. Understanding the physiological changes caused by long-duration microgravity remains a daunting challenge.

Microgravity and the Lung—Prisk GK. J Appl Physiol 2000 Jul;89(1): 385-396.

Although environmental physiologists are readily able to alter many aspects of the environment, it is not possible to remove the effects of gravity on Earth. During the past decade, a series of space flights were conducted in which comprehensive studies of the lung in microgravity (weightlessness) were performed. Stroke volume increases on initial exposure to microgravity and then decreases as circulating blood volume is reduced. Diffusing capacity increases markedly, due to increases in both pulmonary capillary blood volume and membrane diffusing capacity, likely due to more uniform pulmonary perfusion. Both ventilation and

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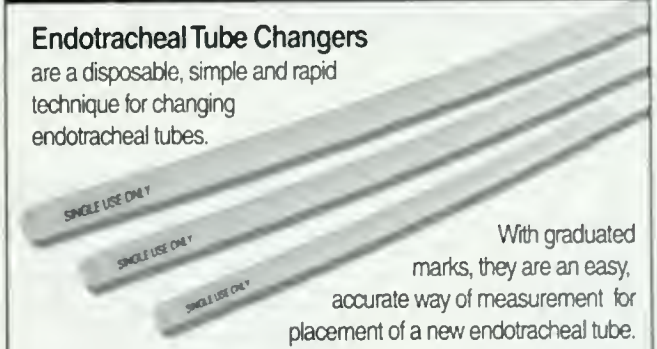

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perfusion become more uniform throughout the lung, although much residual inhomogeneity remains. Despite the improvement in the distribution of both ventilation and perfusion, the range of the ventilation-to-perfusion ratio seen during a normal breath remains unaltered, possibly because of a spatial mismatch between ventilation and perfusion on a small scale. There are unexpected changes in the mixing of gas in the periphery of the lung, and evidence suggests that the intrinsic inhomogeneity of the lung exists at a scale of an acinus or a few acini. In addition, aerosol deposition in the alveolar region is unexpectedly high compared with existing models.

Methylene Blue Improves the Hepatopulmonary Syndrome—Schenk P, Madl C, Rezaie-Majd S, Lehr S, Muller C. Ann Intern Med 2000 Nov 7;133(9):701-706.

BACKGROUND: The hypoxemia of the hepatopulmonary syndrome, seen in patients with severe chronic liver dysfunction, results from widespread pulmonary vasodilation. No established drug therapy is available for this condition. OBJECTIVE: To study the effect of methylene blue, a potent inhibitor of guanylate cyclase, in patients with severe hepatopulmonary syndrome. DESIGN: Open, uncontrolled trial. SETTING: Medical intensive care unit at the university hospital in Vienna, Austria. PATIENTS: 7 patients with advanced cirrhosis and severe hepatopulmonary syndrome with P_{aO_2} of 60 mm Hg or less. INTERVENTION: Insertion of a pulmonary artery catheter and an arterial indwelling catheter; intravenous administration of methylene blue, 3 mg/kg of body weight, over a 15-minute period. MEASUREMENTS: Serial measurements of gas exchange and hemodynamic variables. RESULTS: After methylene blue administration, P_{aO_2} increased in all patients (from a baseline mean ± SD of 58 ± 2.5 mm Hg to 74 ± 11.5 mm Hg 5 hours after infusion; $p = 0.006$) and the alveolar-arterial difference for partial pressure of oxygen ($P_{AO_2} - P_{aO_2}$) decreased in all patients, with a maximum effect achieved after 5 hours (from 49 ± 3.3 mm Hg to 30 ± 10.4 mm Hg; $p = 0.003$); even after 10 hours, $P_{AO_2} - P_{aO_2}$ was still significantly reduced compared with baseline ($p = 0.041$). Oxygenation improved because of reduction in shunt fraction (from 41% ± 3.1% to 25% ± 4.5%; $p < 0.001$). Mean pulmonary artery pressure increased (from 20 ± 5.2 mm Hg to 23 ± 3.6 mm Hg; $p = 0.028$), as did pulmonary vascular resistance (from 58 ± 23 dyne/sec· cm^{-5} to 115 ± 56 dyne/sec· cm^{-5}; $p = 0.012$). Arterial blood pressure did not change significantly. Cardiac output decreased (from 10.6 ± 2.2 L/min to 8.6 ± 2.7 L/min; $p = 0.008$) and systemic vascular resistance increased (from 527 ± 144 dyne/sec· cm^{-5} to 729 ± 222 dyne/sec· cm^{-5}; $p = 0.037$). Heart rate, central venous pressure, and pulmonary capillary wedge pressure remained unchanged. CONCLUSION: Intravenous methylene blue improved hypoxemia and hyperdynamic circulation in patients with liver cirrhosis and severe hepatopulmonary syndrome.

Development and Validation of a Standardized Measure of Activity of Daily Living in Patients with Severe COPD: The London Chest Activity of Daily Living scale (LCADL)—Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Respir Med 2000 Jun;94(6):589-596.

Activities of daily living (ADL) may be severely restricted in patients with COPD and assessment requires evaluation of the impact of disability and handicap on daily life. This study is concerned with the development and validation of a standardized 15-item questionnaire to assess routine ADL. Sixty (33 male, 27 female) patients with severe COPD, mean (SD) FEV_1 0.91 (0.43) L, median (range) age 70 (50-82) years, completed a 59-item ADL list previously generated by open-ended interview and by literature review. Patients also performed the Shuttle Walk Test (SWT), and completed the St George's Respiratory Questionnaire (SGRQ), the Nottingham Extended Activity of Daily Living Questionnaire (EADL) and the Hospital Anxiety and Depression score (HAD). Criteria for item

reduction in the development of The London Chest ADL scale (LCADL) consisted of removal of items where the majority of respondents showed no limitation in the activity (n = 19), where there was no association with perception of global health (n = 9), where an association with age or gender was detected (n = 4), or where items showed poor reliability on test re-test (n = 9). Fifteen items were identified as core activities of daily living. The LCADL was then compared with other measures of health status in these patients. There were good correlations with the SGRQ activity and impact components ($r=0.70$; $p<0.0001$) and ($r=0.58$; $p\leq0.0001$), respectively, and EADL ($r=0.45$; $p<0.001$), and a moderate correlation with HAD anxiety ($r=0.28$; $p<0.03$). There was a significant relationship between the SWT and LCADL ($r=0.58$; $p<0.0001$), suggesting a relationship between impaired exercise performance and lower ADL scores. There was evidence of high internal consistency of the questionnaire with Chronbach's alpha of 0.98. These findings suggest that the LCADL scale is a valid tool for the assessment of ADL in patients with severe COPD.

Patient-Assessed Measures of Health Outcome in Asthma: A Comparison of Four Approaches—Garratt AM, Hutchinson A, Russell I. Respir Med 2000 Jun;94(6):597-606.

The study compares the psychometric properties of four different approaches to patient-assessed health outcomes in asthma, including the Asthma Quality of Life Questionnaire (AQLQ), Newcastle Asthma Symptoms Questionnaire (NASQ), SF-12 and EuroQol. The instruments were administered by means of a self-completed postal questionnaire to 394 patients recruited from general practices in the North East of England. Patients completed a follow-up questionnaire at 6 months. The levels of missing data were assessed and instrument scores compared using correlational analysis. Scores were related to self-reports of smoking behaviour, socioeconomic status and health transition. Responsiveness was assessed using standardized response means. Two hundred and thirty-five patients took part in the study giving a response rate of 59.6%. There was a relatively large amount of missing data for the individualized section of the AQLQ. Correlational analysis provided evidence of convergent validity between the specific instruments; the largest correlation was found between NASQ scores and the asthma symptoms scale of the AQLQ ($r = 0.84$). The NASQ was found to be the most powerful at discriminating between smokers and non-smokers. All four instruments were linearly related to self-reported asthma transition ($p<0.05$); the specific instruments having the strongest association. The specific instruments showed good levels of responsiveness with the NASQ producing a large SRM of 0.82. SRMs for the AQLQ were of a moderate to large size (0.32-0.77) and the SRMs for the SF-12 and EuroQol were of a small size. The two specific instruments are capable of greater levels of discrimination between groups of patients and are more responsive to changes in health than the generic SF-12 and EuroQol. The greater responsiveness of the NASQ is probably due to its focus being restricted to symptoms of asthma compared to the broader focus of the AQLQ domains. The NASQ has a strong relationship with the AQLQ and is a more practical instrument that is more acceptable to patients. However, the AQLQ does measure broader patient concerns. The SF-12 and EuroQol have greater potential to capture side-effects and have wider scope for application in economic evaluation.

Prescribing Patterns for Asthma by General Practitioners in Six European Countries—Jepson G, Butler T, Gregory D, Jones K. Respir Med 2000 Jun;94(6):578-583.

To assess the level of concordance with international consensus on asthma management, we compared primary care prescribing patterns for asthma in different European countries. A prospective study of prescription items with an associated diagnostic label of asthma in patient consultations with a total of 235 general practitioners (GPs) from Belgium, England, Ireland, Italy, Northern Ireland, Portugal, Scotland and Spain was performed. A total of 101,544 consecutive consultations were recorded in autumns 1994 and 1995 of which 3595 (3.5%) were for patients with asthma and 3243 (3.2%) were for patients receiving a prescription for asthma. Overall, asthma consultations varied from 1.8% in Italy to 5.8% in Ireland (mean 3.4%, SD 1.6). Prescribed inhaled medications for children varied from 72% of the total asthma prescriptions in Ireland and Portugal to 82% in Northern Ireland (mean 79%, SD 8.1) and for adults 55% in Italy to 85% in Spain (mean 70%, SD 10). Inhaled corticosteroid usage for adults varied from 14% in Italy to 31% in Northern Ireland (mean 24%, SD 6.4). For children, β_2-agonist use varied from 24% in Italy to 67% in Spain (mean 45%, SD 13). Despite publication of international guidelines for the management of asthma, inter-country prescribing practices vary considerably and could be improved. The frequency of use of asthma as a diagnostic label also varies markedly.

Equivalent Therapeutic Ratio of Salbutamol Given by Turbuhaler and Diskus—Arvidsson P, Mellen A, Palmqvist M, Lotvall J. Respir Med 2000 Jun;94(6):574-577.

Some inhalers have been claimed to give better deposition, resulting in higher efficacy. In a previous study we did not find any evidence of different potency of salbutamol given either via pMDI or Turbuhaler. The aim of the present study was to compare the efficacy and safety of salbutamol given via Diskus or Turbuhaler. Twenty-five asthmatics with step-wise reversible airflow obstruction (total reversibility of at least 15%) were included in a randomized, double-dummy, placebo-controlled cross-over study. On each study day, the patients were given placebo repeatedly, or cumulative doses of 200, 400, 800, 1600 and 3200 microg salbutamol given via either device (double-blind, placebo-controlled). Salbutamol caused a dose-related increase in FEV_1 when given by Diskus or Turbuhaler. The improvement in FEV_1 was similar regardless of whether salbutamol was given via Diskus or Turbuhaler, at equivalent microgram doses. After a total cumulative dose of 3200 microg, mean FEV_1 for Diskus was 2.46 L (change from baseline of 20.5%), for Turbuhaler 2.50 L (change from baseline 24.6%) and for placebo 2.11 L (3% change from baseline). After correcting for different baseline differences, the percentage difference between Diskus and Turbuhaler was -1.8% ($p = 0.2$). Systemic effects (potassium and heart rate) did not differ between Diskus or Turbuhaler. We conclude that the efficacy of salbutamol given at equivalent microgram doses, as well as side-effects, are comparable when the drug is given via Diskus or Turbuhaler. The present data shows that salbutamol given by these devices have similar therapeutic ratios.

The Accuracy of Subjective Sleep Time in Sleep Apnoea Recordings—Franklin KA, Svanborg E. Respir Med 2000 Jun;94(6):569-573.

Total sleep time is important in investigations of obstructive sleep apnoea, since the diagnosis is usually based on the average number of apnoeas per hour of sleep. Sleep estimates instead of exact EEG-recorded total sleep time is often used in the clinical setting. However, an overestimated sleep time would underestimate the degree of the disease and vice versa. The purpose of this study was to investigate the accuracy of subjective sleep time and time-in-bed as sleep estimates. One hundred patients undergoing diagnostic polysomnography for suspected obstructive sleep apnoea were asked to estimate their sleep time in a questionnaire. Seventy-five patients were diagnosed as suffering from obstructive sleep apnoea syndrome. The mean difference between self-scored and EEG-recorded total sleep time was 4 ± 74 min. However, 30% scored with a difference greater than 1 h. The intra-class correlation coefficient was fair (0.58, CI: 0.43-0.70). Fifty-three patients overestimated their sleep time and 47 patients underestimated it. All but four patients underestimated their number of awakenings ($p<0.001$). The mean difference between time-in-bed and EEG-recorded total sleep time was 110 ± 63 min. This

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difference was significantly larger than the difference between subjective sleep time and EEG-recorded total sleep time ($p<0.001$). The intra-class correlation coefficient was poor (0.38, CI: 0.20-0.54). Mean AHI was 27 ± 27 using subjective sleep time and did not change significantly compared with the mean AHI of 25 ± 21 based on EEG-recorded total sleep time. Mean AHI decreased significantly to 20 ± 17 ($p<0.001$) when time-in-bed was used. In conclusion, 'time-in-bed' time is a poor predictor of total sleep time and should not be used when calculating the apnoea-hypopnoea index. Subjective sleep time is better as an approximation, but the individual differences are large.

A Demand Valve Device Decreases Exhaust Nitric Oxide and Nitrogen Dioxide by Nitric Oxide Inhalation with a Nasal Cannula in the Human—Saito T, Ninomiya H, Ohtsu I, Inoue M, Uchida Y, Hasegawa S. Respir Med 2000 Jun;94(6):542-548.

To improve patients' quality of life and decrease pollution risks to medical personnel, we tested the usefulness of a nitric oxide (NO) inhalation system consisting of a nasal cannula and a demand valve in an open circuit system. To estimate the content of NO entering the lung with the open system, concentrations of NO and nitrogen dioxide (NO_2) were measured in a mechanical lung model, and then nitrocylhaemoglobin (NO-Hb), methaemoglobin (Met-Hb), and nitrite (NO_2^-) + nitrate (NO_3^-) concentrations in venous blood were measured in eight healthy subjects. Exhaust NO and NO_2 in the open system were also observed in 14 healthy subjects. In the lung model, NO concentration delivered with the open system was approximately 1/11 of that in the gas tank. Increases in Met-Hb and NO_2^- + NO_3^- with the open system showed that the concentration of delivered NO was approximately 1/9 of that in the gas tank. The open system reduced exhaust NO to 1/10 in human subjects. These data suggest that this NO inhalation system delivers sufficient NO to spontaneously breathing patients. In addition, these findings indicate that there is little environmental toxicity associated with the open circuit system.

Asthma on the Job: Work-Related Factors in New-Onset Asthma and in Exacerbations of Pre-Existing Asthma—Toren K, Brisman J, Olin AC, Blanc PD. Respir Med 2000 Jun;94(6):529-535.

Occupational asthma (OA) can be defined as variable airways narrowing causally related to exposure in the working environment to airborne dusts, gases, vapours or fumes. There are many agents in the work-place that can induce asthma or cause substantial deterioration in pre-existing asthma. It has been estimated that 5-15% of adult-onset asthma can be attributed to occupational exposures. Hence adult patients, especially those with new-onset asthma, must be investigated with regard to occupational risk factors for disease. The prognosis for OA is improved if the causal exposure is controlled either by controlling the exposure at the workplace or by moving the patient out of the workplace.

Pharmaceutical Transition to Non-CFC Pressurized Metered Dose Inhalers—Cripps A, Riebe M, Schulze M, Woodhouse R. Respir Med 2000 Jun;94 Suppl B:S3-S9.

The production of ozone-depleting chlorofluorocarbons (CFCs) was discontinued on 1 January 1996 for all uses deemed non-essential under the Montreal Protocol. However, the use of CFCs as propellants in pressurized metered dose inhalers (pMDIs) was classed as essential, providing an exemption from the agreement. Following extensive research, the hydrofluoroalkanes (HFA) 134a and 227 were identified as the only suitable replacements for CFC propellants in pMDIs. The drug delivery of pMDIs formulated with HFA 134a as a propellant and containing either salbutamol (100 microg per actuation) or fluticasone propionate (125 and 250 microg per actuation) have been assessed for dose uniformity and particle size distribution. All of the HFA 134a pMDIs delivered doses throughout the life of the canisters that were reproducible and within specified regulatory requirements. Each of the products provided an emitted dose which was within ± 25% of the mean value indicating accurate and consistent dosing (93, 112 and 221 microg per metered dose for the salbutamol 100 microg and fluticasone propionate 125 and 250 microg HFA 134a pMDIs, respectively). These findings were unaffected by changing the storage orientation of the pMDI or by using the device in a manner designed to simulate typical patient use. The particle size distributions of HFA 134a pMDI doses did not differ significantly from those of the corresponding CFC pMDIs. As a result of the similar pharmaceutical performance, it is unnecessary to change the label claim dose of active drug when making the transition from a CFC to an HFA 134a pMDI for salbutamol (Ventolin) and fluticasone propionate (Flixotide). A seamless transition to non-CFC pMDIs will help to maintain the confidence of patients and healthcare professionals in asthma therapy.

Effect of Gravity on Aerosol Dispersion and Deposition in the Human Lung after Periods of Breath Holding—Darquenne C, Paiva M, Prisk GK. J Appl Physiol 2000 Nov;89(5):1787-1792.

To determine the extent of the role that gravity plays in dispersion and deposition during breath holds, we performed aerosol bolus inhalations of 1-μ-diameter particles followed by breath holds of various lengths on four subjects on the ground (1G) and during short periods of microgravity (μG). Boluses of approximately 70 mL were inhaled to penetration volumes (V_p) of 150 and 500 mL, at a constant flow rate of approximately 0.45 L/s. Aerosol concentration and flow rate were continuously measured at the mouth. Aerosol deposition and dispersion were calculated from these data. Deposition was independent of breath-hold time at both V_p in μG, whereas, in 1G, deposition increased with increasing breath hold time. At V_p = 150 mL, dispersion was similar at both gravity levels and increased with breath hold time. At V_p = 500 mL, dispersion in 1G was always significantly higher than in μG. The data provide direct evidence that gravitational sedimentation is the main mechanism of deposition and dispersion during breath holds. The data also suggest that cardiogenic mixing and turbulent mixing contribute to deposition and dispersion at shallow V_p.

Simplified Rat Intubation Using a New Oropharyngeal Intubation Wedge—Jou IM, Tsai YT, Tsai CL, Wu MH, Chang HY, Wang NS. J Appl Physiol 2000 Nov;89(5):1766-1770.

Our new oropharyngeal intubation wedge made from a plastic 3-mL syringe has been used successfully for the expansion of the oropharyngeal cavity and visualization of vocal cords for endotracheal intubation in the rat. All the animals we used tolerated the intubation and ventilation procedures in a series of experiments. After the proper setting of the respirator, vital signs were maintained within normal range. The postmortem examination and measurements in the upper airway confirmed that the endotracheal tube was properly sited and also demonstrated the precise size of the device that should be used. The main advantages of this method include low cost, simplicity, and reliability. Furthermore, because no expensive, elaborate, difficult-to-operate, or hard-to-get special equipment is needed, this technique can be used in every laboratory.

A Human Acinar Structure for Simulation of Realistic Alveolar Plateau Slopes—Dutrieue B, Vanholsbeeck F, Verbanck S, Paiva M. J Appl Physiol 2000 Nov;89(5):1859-1867.

We simulated the intra-acinar contribution to phase III slope (S_{acin}) for gases of differing diffusivities (He and SF_6) by solving equations of diffusive and convective gas transport in multi-branch-point models (MBPM) of the human acinus. We first conducted a sensitivity study of S_{acin} to asymmetry and its variability in successive generations. S_{acin} increases were greatest when asymmetry and variability of asymmetry

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were increased at the level of the respiratory bronchioles (generations 17-18) for He and at the level of the alveolar ducts (generations 20-21) for SF_6, corresponding to the location of their respective diffusion fronts. On the basis of this sensitivity study and in keeping with reported acinar morphometry, we built a MBPM that actually reproduced experimental S_{acin} values obtained in normal subjects for He, N_2, and SF_6. Ten variants of such a MBPM were constructed to estimate intrinsic S_{acin} variability owing to peripheral lung structure. The realistic simulation of S_{acin} in the normal lung and the understanding of how asymmetry affects S_{acin} for different diffusivity gases make S_{acin} a powerful tool to detect structural alterations at different depths in the lung periphery.

Size Distribution of Recruited Alveolar Volumes in Airway Reopening—Suki B, Alencar AM, Tolnai J, Asztalos T, Petak F, Sujeer MK, et al. J Appl Physiol 2000 Nov;89(5):2030-2040.

In 11 isolated dog lung lobes, we studied the size distribution of recruited alveolar volumes that become available for gas exchange during inflation from the collapsed state. Three catheters were wedged into 2-mm-diameter airways at total lung capacity. Small-amplitude pseudorandom pressure oscillations between 1 and 47 Hz were led into the catheters, and the input impedances of the regions subtended by the catheters were continuously recorded using a wave tube technique during inflation from -5 cm H_2O transpulmonary pressure to total lung capacity. The impedance data were fit with a model to obtain regional tissue elastance (Eti) as a function of inflation. First, Eti was high and decreased in discrete jumps as more groups of alveoli were recruited. By assuming that the number of opened alveoli is inversely proportional to Eti, we calculated from the jumps in Eti the distribution of the discrete increments in the number of opened alveoli. This distribution was in good agreement with model simulations in which airways open in cascade or avalanches. Implications for mechanical ventilation may be found in these results.

Effect of Expiratory Resistive Loading on the Noninvasive Tension-Time Index in COPD—Thompson WH, Carvalho P, Souza JP, Charan NB. J Appl Physiol 2000 Nov;89(5):2007-2014.

Expiratory resistive loading (ERL) is used by chronic obstructive pulmonary disease (COPD) patients to improve respiratory function. We, therefore, used a noninvasive tension-time index of the inspiratory muscles (TT_{mus} = $1/PI_{max}$ × TI/TT, where I is mean inspiratory pressure estimated from the mouth occlusion pressure, PI_{max} is maximal inspiratory pressure, TI is inspiratory time, and TT is total respiratory cycle time) to better define the effect of ERL on COPD patients. To accomplish this, we measured airway pressures, mouth occlusion pressure, respiratory cycle flow rates, and functional residual capacity (FRC) in 14 COPD patients and 10 normal subjects with and without the application of ERL. TT_{mus} was then calculated and found to drop in both COPD and normal subjects ($p < 0.05$). The decline in TT_{mus} in both groups resulted solely from a prolongation of expiratory time with ERL ($p < 0.001$ for COPD, $p < 0.05$ for normal subjects). In contrast to the COPD patients, normal subjects had an elevation in I and FRC, thus minimizing the decline in TT_{mus}. In conclusion, ERL reduces the potential for inspiratory muscle fatigue in COPD by reducing TI/TT without affecting FRC and I.

Association between Cigarette Smoking and Anxiety Disorders during Adolescence and Early Adulthood—Johnson JG, Cohen P, Pine DS, Klein DF, Kasen S, Brook JS. JAMA 2000 Nov 8;284(18):2348-2351.

CONTEXT: Cigarette smoking is associated with some anxiety disorders, but the direction of the association between smoking and specific anxiety disorders has not been determined. OBJECTIVE: To investigate the longitudinal association between cigarette smoking and anxiety disorders among adolescents and young adults. DESIGN: The Children in the Community Study, a prospective longitudinal investigation. SETTING AND PARTICIPANTS: Community-based sample of 688 youths (51% female) from upstate New York interviewed in the years 1985-1986, at a mean age of 16 years, and in the years 1991-1993, at a mean age of 22 years. MAIN OUTCOME MEASURE: Participant cigarette smoking and psychiatric disorders in adolescence and early adulthood, measured by age-appropriate versions of the Diagnostic Interview Schedule for Children. RESULTS: Heavy cigarette smoking (≥ 20 cigarettes/d) during adolescence was associated with higher risk of agoraphobia (10.3% vs 1.8%; odds ratio [OR], 6.79; 95% confidence interval [CI], 1.53-30.17), generalized anxiety disorder (20.5% vs 3.7%; OR, 5.53; 95% CI, 1.84-16.66), and panic disorder (7.7% vs 0.6%; OR, 15.58; 95% CI, 2.31-105.14) during early adulthood after controlling for age, sex, difficult childhood temperament; alcohol and drug use, anxiety, and depressive disorders during adolescence; and parental smoking, educational level, and psychopathology. Anxiety disorders during adolescence were not significantly associated with chronic cigarette smoking during early adulthood. Fourteen percent and 15% of participants with and without anxiety during adolescence, respectively, smoked at least 20 cigarettes per day during early adulthood (OR, 0.88; 95% CI, 0.36-2.14). CONCLUSION: Our results suggest that cigarette smoking may increase risk of certain anxiety disorders during late adolescence and early adulthood.

Treatment of Acute Hypoxemic Nonhypercapnic Respiratory Insufficiency with Continuous Positive Airway Pressure Delivered by a Face Mask: A Randomized Controlled Trial—Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, et al. JAMA 2000 Nov 8;284(18):2352-2360.

CONTEXT: Continuous positive airway pressure (CPAP) is widely used in the belief that it may reduce the need for intubation and mechanical ventilation in patients with acute hypoxemic respiratory insufficiency. OBJECTIVE: To compare the physiologic effects and the clinical efficacy of CPAP vs standard oxygen therapy in patients with acute hypoxemic, nonhypercapnic respiratory insufficiency. DESIGN, SETTING, AND PATIENTS: Randomized, concealed, and unblinded trial of 123 consecutive adult patients who were admitted to 6 intensive care units between September 1997 and January 1999 with a P_{aO_2}/F_{IO_2} ratio of 300 mm Hg or less due to bilateral pulmonary edema (n = 102 with acute lung injury and n = 21 with cardiac disease). INTERVENTIONS: Patients were randomly assigned to receive oxygen therapy alone (n = 61) or oxygen therapy plus CPAP (n = 62). MAIN OUTCOME MEASURES: Improvement in P_{aO_2}/F_{IO_2} ratio, rate of endotracheal intubation at any time during the study, adverse events, length of hospital stay, mortality, and duration of ventilatory assistance, compared between the CPAP and standard treatment groups. RESULTS: Among the CPAP vs standard therapy groups, respectively, causes of respiratory failure (pneumonia, 54% and 55%), presence of cardiac disease (33% and 35%), severity at admission, and hypoxemia (median [5th-95th percentile] P_{aO_2}/F_{IO_2} ratio, 140 [59-288] mm Hg vs 148 [62-283] mm Hg; p =0.43) were similarly distributed. After 1 hour of treatment, subjective responses to treatment ($p<0.001$) and median (5th-95th percentile) P_{aO_2}/F_{IO_2} ratios were greater with CPAP (203 [45-431] mm Hg vs 151 [73-482] mm Hg; p =0.02). No further difference in respiratory indices was observed between the groups. Treatment with CPAP failed to reduce the endotracheal intubation rate (21 [34%] vs 24 [39%] in the standard therapy group; p =0.53), hospital mortality (19 [31%] vs 18 [30%]; p =0.89), or median (5th-95th percentile) intensive care unit length of stay (6.5 [1-57] days vs 6.0 [1-36] days; p =0.43). A higher number of adverse events occurred with CPAP treatment (18 vs 6; p =0.01). CONCLUSION: In this study, despite early physiologic improvement, CPAP neither reduced the need for intubation nor improved outcomes in patients with acute hypoxemic, nonhypercapnic respiratory insufficiency primarily due to acute lung injury.

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Association of Noninvasive Ventilation with Nosocomial Infections and Survival in Critically Ill Patients—Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, et al. JAMA 2000 Nov 8;284(18): 2361-2367.

CONTEXT: Invasive life-support techniques are a major risk factor for nosocomial infection. Noninvasive ventilation (NIV) can be used to avoid endotracheal intubation and may reduce morbidity among patients in intensive care units (ICUs). OBJECTIVE: To determine whether the use of NIV is associated with decreased risk of nosocomial infections and improved survival in everyday clinical practice among patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) or hypercapnic cardiogenic pulmonary edema (CPE). DESIGN AND SETTING: Matched case-control study conducted in the medical ICU of a French university hospital from January 1996 through March 1998. PATIENTS: Fifty patients with acute exacerbation of COPD or severe CPE who were treated with NIV for at least 2 hours and 50 patients treated with mechanical ventilation between 1993 and 1998 (controls), matched on diagnosis, Simplified Acute Physiology Score II, Logistic Organ Dysfunction score, age, and no contraindication to NIV. MAIN OUTCOME MEASURES: Rates of nosocomial infections, antibiotic use, lengths of ventilatory support and of ICU stay, ICU mortality, compared between cases and controls. RESULTS: Rates of nosocomial infections and of nosocomial pneumonia were significantly lower in patients who received NIV than those treated with mechanical ventilation (18% vs 60% and 8% vs 22%; $p<0.001$ and $p=0.04$, respectively). Similarly, the daily risk of acquiring an infection (19 vs 39 episodes per 1000 patient-days; $p=0.05$), proportion of patients receiving antibiotics for nosocomial infection (8% vs 26%; $p=0.01$), mean (SD) duration of ventilation (6 [6] vs 10 [12] days; $p=0.01$), mean (SD) length of ICU stay (9 [7] vs 15 [14] days; $p=0.02$), and crude mortality (4% vs 26%; $p=0.002$) were all lower among patients who received NIV than those treated with mechanical ventilation. CONCLUSIONS: Use of NIV instead of mechanical ventilation is associated with a lower risk of nosocomial infections, less antibiotic use, shorter length of ICU stay, and lower mortality.

HIV Seroprevalence by Anonymous Testing in Patients with *Mycobacterium Tuberculosis* and in Tuberculosis Contacts—Bowen EF, Rice PS, Cooke NT, Whitfield RJ, Rayner CF. Lancet 2000 Oct 28; 356(9240):1488-1489.

Having witnessed a large increase in *Mycobacterium tuberculosis* notifications in south London, we wanted to ascertain the prevalence of HIV and tuberculosis co-infection in our patients. All patients with tuberculosis and their contacts were anonymously tested for HIV in blood and saliva, respectively. 11.4% of patients (from various demographic groups) with tuberculosis who attend chest clinics in south London are HIV positive. In addition, 5% of individuals seen in the tuberculosis contact screening clinics and 4% new entrants are HIV positive. All patients with *Mycobacterium tuberculosis*, irrespective of background, should be urged to have an HIV test.

Sputum Eosinophilia and Short-Term Response to Prednisolone in Chronic Obstructive Pulmonary Disease: A Randomised Controlled Trial—Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, Pavord ID. Lancet 2000 Oct 28;356(9240):1480-1485.

BACKGROUND: Some patients with chronic obstructive pulmonary disease (COPD) respond to corticosteroid therapy. Whether these patients have different airway pathology from other COPD patients is unclear. We tested the hypothesis that response to prednisolone is related to the presence of eosinophilic airway inflammation. METHODS: We did a randomised, double-blind, crossover trial. Patients who had COPD treated with bronchodilators only were assigned placebo and 30 mg prednisolone daily for 2 weeks each, in a random order, separated by a 4-week washout period. Before and after each treatment period, we assessed patients with spirometry, symptom scores, the chronic respiratory disease questionnaire (CRQ), incremental shuttle walk test, and induced sputum. Analysis was done by intention to treat. FINDINGS: 83 patients were recruited, of whom 67 were randomised. The geometric mean sputum eosinophil count fell significantly after prednisolone (from 2.4% to 0.4%; mean difference six-fold [95% CI 3.1-11.4]) but not after placebo. Other sputum cell counts did not change. After stratification into tertiles by baseline eosinophil count, postbronchodilator forced expiratory volume in 1 s (FEV_1) and total scores on the CRQ improved progressively after prednisolone from the lowest to the highest eosinophilic tertile, compared with placebo. The mean change in postbronchodilator FEV_1, total CRQ score, and shuttle walk distance with prednisolone compared with placebo in the highest tertile was 0.19 L (0.06-0.32), 0.62 (0.31-0.93), and 20 m (5-35), respectively. INTERPRETATION: Our findings suggest that eosinophilic airway inflammation contributes to airflow obstruction and symptoms in some patients with COPD and that the short-term effects of prednisolone are due to modification of this feature of the inflammatory response. The possibility that sputum eosinophilia identifies a subgroup of patients who particularly respond to long-term treatment with inhaled corticosteroids should be investigated.

Inhaled Nitric Oxide and Prevention of Pulmonary Hypertension after Congenital Heart Surgery: A Randomised Double-Blind Study—Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. Lancet 2000 Oct 28;356(9240):1464-1469.

BACKGROUND: Pulmonary hypertensive crises (PHTC) are a major cause of morbidity and mortality after congenital heart surgery. Inhaled nitric oxide is frequently used as rescue therapy. We did a randomised double-blind study to investigate the role of routinely administered inhaled nitric oxide to prevent pulmonary hypertension in infants at high risk. METHODS: We enrolled 124 infants (64 male, 60 female; median age 3 months [IQR 1-5]), 76% with large ventricular or atrioventricular septal defects, who had high pulmonary flow, pressure, or both, and were undergoing corrective surgery for congenital heart disease. They were randomly assigned continuous low-dose inhaled nitric oxide (n=63) or placebo (n=61) from surgery until just before extubation. We measured the numbers of PHTC, time on study gas, and hours spent in intensive care. Analysis was done by intention to treat. FINDINGS: Compared with placebo, infants receiving inhaled nitric oxide had fewer PHTC (median four [IQR 0-12] vs seven [1-19]; relative risk, unadjusted 0.66, $p<0.001$, adjusted for dispersion 0.65, $p=0.045$) and shorter times until criteria for extubation were met (80 [38-121] vs 112 h [63-164], $p=0.019$). Time taken to wean infants off study gas was 35% longer in the nitric oxide group than in the placebo group ($p=0.19$), but the total time on the study gas was still 30 h shorter for the nitric oxide group (87 [43-125] vs 117 h [67-168], $p=0.023$). No important toxic effects arose. INTERPRETATION: In infants at high risk of pulmonary hypertension, routine use of inhaled nitric oxide after congenital heart surgery can lessen the risk of pulmonary hypertensive crises and shorten the postoperative course, with no toxic effects.

Fine Particulate Air Pollution and Mortality in 20 U.S. Cities, 1987-1994—Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. N Engl J Med 2000 Dec 14;343(24):1742-1749.

BACKGROUND: Air pollution in cities has been linked to increased rates of mortality and morbidity in developed and developing countries. Although these findings have helped lead to a tightening of air-quality standards, their validity with respect to public health has been questioned. METHODS: We assessed the effects of five major outdoor-air pollutants on daily mortality rates in 20 of the largest cities and metropolitan areas in the United States from 1987 to 1994. The pollutants were particulate matter that is less than 10 microm in aerodynamic diameter (PM_{10}),

ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide. We used a two-stage analytic approach that pooled data from multiple locations. RESULTS: After taking into account potential confounding by other pollutants, we found consistent evidence that the level of PM_{10} is associated with the rate of death from all causes and from cardiovascular and respiratory illnesses. The estimated increase in the relative rate of death from all causes was 0.51 percent (95 percent posterior interval, 0.07 to 0.93 percent) for each increase in the PM_{10} level of 10 microg per cubic meter. The estimated increase in the relative rate of death from cardiovascular and respiratory causes was 0.68 percent (95 percent posterior interval, 0.20 to 1.16 percent) for each increase in the PM_{10} level of 10 microg per cubic meter. There was weaker evidence that increases in ozone levels increased the relative rates of death during the summer, when ozone levels are highest, but not during the winter. Levels of the other pollutants were not significantly related to the mortality rate. CONCLUSIONS: There is consistent evidence that the levels of fine particulate matter in the air are associated with the risk of death from all causes and from cardiovascular and respiratory illnesses. These findings strengthen the rationale for controlling the levels of respirable particles in outdoor air.

Association of the California Tobacco Control Program with Declines in Cigarette Consumption and Mortality from Heart Disease—Fichtenberg CM, Glantz SA. N Engl J Med 2000 Dec 14;343(24):1772-1777.

BACKGROUND: The California Tobacco Control Program, a large, aggressive antitobacco program implemented in 1989 and funded by a voter-enacted cigarette surtax, accelerated the decline in cigarette consumption and in the prevalence of smoking in California. Since the excess risk of heart disease falls rapidly after the cessation of smoking, we tested the hypothesis that this program was associated with lower rates of death from heart disease. METHODS: Data on per capita cigarette consumption and age-adjusted rates of death from heart disease in California and the United States from 1980 to 1997 were fitted in multiple regression analyses. The regression analyses included the rates in the rest of the United States and variables that allowed for changes in the rates after 1988, when the tobacco-control program was approved, and after 1992, when the program was cut back. RESULTS: Between 1989 and 1992, the rates of decline in per capita cigarette consumption and mortality from heart disease in California, relative to the rest of the United States, were significantly greater than the pre-1989 rates, by 2.72 packs per year per year ($p=0.001$) and by 2.93 deaths per year per 100,000 population per year ($p<0.001$). These rates of decline were reduced (by 2.05 packs per year per year [$p=0.04$], and by 1.71 deaths per year per 100,000 population per year [$p=0.03$]) when the program was cut back, beginning in 1992. Despite these problems, the program was associated with 33,300 fewer deaths from heart disease between 1989 and 1997 than the number that would have been expected if the earlier trend in mortality from heart disease in California relative to the rest of the United States had continued. The diminished effectiveness of the program after 1992 was associated with 8300 more deaths than would have been expected had its initial effectiveness been maintained. CONCLUSIONS: A large and aggressive tobacco-control program is associated with a reduction in deaths from heart disease in the short run.

Dying Patients in the Intensive Care Unit: Forgoing Treatment, Maintaining Care—Faber-Langendoen K, Lanken PN. Ann Intern Med 2000 Dec 5;133(11):886-893.

End-of-life care of patients in the intensive care unit (ICU) often requires dramatic shifts in attitudes and interventions, from traditional intensive rescue care to intensive palliative care. The care of patients dying in ICUs raises both clinical and ethical difficulties. Because fewer ICU patients are able to make decisions about withdrawing treatment, careful attention must be paid to previously expressed preferences and surrogate input. Cultural and spiritual values of patients and families may differ markedly from those of clinicians. Although prognostic models are increasingly able to predict mortality rates for groups of ICU patients, their usefulness in guiding specific decisions to forgo treatment has not been established. When a decision to forgo treatment is made, the focus should be on specifying the patient's goals of care and assessing all treatments in light of these goals; interventions that do not contribute to the patient's goals should be discontinued. Symptoms accompanying withdrawal of life support can almost always be controlled with appropriate palliative measures. After ICU interventions are forgone, patient comfort must be the paramount objective. Whether in the ICU or elsewhere, hospitals have an ethical obligation to provide settings that offer dignified, compassionate, and skilled care.

Outcomes and Cost-Effectiveness of Ventilator Support and Aggressive Care for Patients with Acute Respiratory Failure due to Pneumonia or Acute Respiratory Distress Syndrome—Hamel MB, Phillips RS, Davis RB, Teno J, Connors AF, Desbiens N, et al. Am J Med 2000 Dec 1;109(8):614-620.

PURPOSE: Many patients with acute respiratory failure die despite prolonged and costly treatment. Our objective was to estimate the cost-effectiveness of providing rather than withholding mechanical ventilation and intensive care for patients with acute respiratory failure due to pneumonia or acute respiratory distress syndrome. SUBJECTS AND METHODS: We studied 1,005 patients enrolled in a five-center study of seriously ill patients (the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments [SUPPORT]) with acute respiratory failure (pneumonia or acute respiratory distress syndrome and an Acute Physiology Score ≥ 10) who required ventilator support. We estimated life expectancy based on long-term follow-up of SUPPORT patients. Utilities were estimated using time-tradeoff questions. Costs (in 1998 dollars) were based on hospital fiscal data and Medicare data. RESULTS: Of the 963 patients who received ventilator support, 48% survived for at least 6 months. At 6 months, survivors reported a median of 1 dependence in activities of daily living, and 72% rated their quality of life as good, very good, or excellent. Among the 42 patients in whom ventilator support was withheld, the median survival was 3 days. Among patients whose estimated probability of surviving at least 2 months from the time of ventilator support ("prognostic estimate") was 70% or more, the incremental cost per quality-adjusted life-year (QALY) saved by providing rather than withholding ventilator support and aggressive care was $29,000. For medium-risk patients (prognostic estimate 51% to 70%), the incremental cost-effectiveness was $44,000 per QALY, and for high-risk patients (prognostic estimate $\leq 50\%$), it was $110,000 per QALY. When assumptions were varied from 50% to 200% of baseline estimates, the results ranged from $19,000 to $48,000 for low-risk patients, from $29,000 to $76, 000 for medium-risk patients, and from $67,000 to $200,000 for high-risk patients. CONCLUSIONS: Ventilator support and intensive care for acute respiratory failure due to pneumonia or acute respiratory distress syndrome are relatively cost-effective for patients with $>50\%$ probability of surviving 2 months. However, for patients with an expected 2-month survival $\leq 50\%$, the cost per QALY is more than threefold greater at $>$$100,000.

Mechanisms of Hypertension in Patients with Chronic Obstructive Pulmonary Disease and Acute Respiratory Failure—Fontana F, Bernardi P, Tartuferi L, Boschi S, De Iasio R, Merlo Pich E. Am J Med 2000 Dec 1;109(8):621-627.

PURPOSE: To investigate the effects of hypoxemia, hypercapnia, and cardiovascular hormones (norepinephrine, endothelin [1], and atrial natriuretic factor) on blood pressure during acute respiratory failure. PATIENTS AND METHODS: Patients with chronic obstructive pulmonary

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disease and acute respiratory failure were divided into four groups of 10 patients each: hypoxemia-normocapnia, hypoxemia-hypercapnia, hypoxemia-hypocapnia, and normoxemia-hypercapnia. Plasma norepinephrine levels were determined by high-performance liquid chromatography with electrochemical detection. Plasma endothelin-1 and atrial natriuretic factor levels were radioimmunoassayed after chromatographic preextraction. RESULTS: Systolic blood pressure and cardiovascular hormone levels were greater in patients with hypercapnia (whether or not they also had hypoxemia) than in those with normocapnia and hypoxemia. For example, in patients with hypercapnia and normoxemia, the mean (± SD) systolic blood pressure was 183 ±31 mm Hg and the mean norepinephrine level was 494 ± 107 pg/mL, as compared with 150 ± 6 mm Hg and 243 ± 58 pg/mL in those with normocapnia and hypoxemia (both $p < 0.05$). Similar results were seen for endothelin-1 and atrial natriuretic factor levels, and for the comparisons of hypoxemic patients who were hypercapnic with those who were normocapnic. CONCLUSIONS: These results suggest that blood carbon dioxide levels, rather than oxygen levels, are responsible for hypertension during acute respiratory failure, perhaps as a result of enhanced sympatho-adrenergic activity.

Current and Projected Workforce Requirements for Care of the Critically Ill and Patients with Pulmonary Disease: Can We Meet the Requirements of an Aging Population?—Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. JAMA 2000 Dec 6;284(21):2762-2770.

CONTEXT: Two important areas of medicine, care of the critically ill and management of pulmonary disease, are likely to be influenced by the aging of the US population. OBJECTIVE: To estimate current and future requirements for adult critical care and pulmonary medicine physicians in the United States. DESIGN, SETTING, AND PARTICIPANTS: Analysis of existing population, patient, and hospital data sets and prospective, nationally representative surveys of intensive care unit (ICU) directors (n = 393) and critical care specialists (intensivists) and pulmonary specialists (pulmonologists) (n = 421), conducted from 1996 to 1999. MAIN OUTCOME MEASURES: Influence of patient, physician, regional, hospital, and payer characteristics on current practice patterns; forecasted future supply of and demand for specialist care through 2030. Separate models for critical care and pulmonary disease. Base-case projections with sensitivity analyses to estimate the impact of future changes in training and retirement, disease prevalence and management, and health care reform initiatives. RESULTS: In 1997, intensivists provided care to 36.8% of all ICU patients. Care in the ICU was provided more commonly by intensivists in regions with high managed care penetration. The current ratio of supply to demand is forecast to remain in rough equilibrium until 2007. Subsequently, demand will grow rapidly while supply will remain near constant, yielding a shortfall of specialist hours equal to 22% of demand by 2020 and 35% by 2030, primarily because of the aging of the US population. Sensitivity analyses suggest that the spread of current health care reform initiatives will either have no effect or worsen this shortfall. A shortfall of pulmonologist time will also occur before 2007 and increase to 35% by 2020 and 46% by 2030. CONCLUSIONS: We forecast that the proportion of care provided by intensivists and pulmonologists in the United States will decrease below current standards in less than 10 years. While current health care reform initiatives and modification of existing practice patterns may temporarily forestall this problem, most anticipated effects are minor in comparison with the growing disease burden created by the aging US population.

"Hospital at Home" versus Hospital Care in Patients with Exacerbations of Chronic Obstructive Pulmonary Disease: Prospective Randomised Controlled Trial—Davies L, Wilkinson M, Bonner S, Calverley PM, Angus RM. BMJ 2000 Nov 18;321(7271):1265-1268.

OBJECTIVES: To compare "hospital at home" and hospital care as an inpatient in acute exacerbations of chronic obstructive pulmonary disease. DESIGN: Prospective randomised controlled trial with three months' follow up. SETTING: University teaching hospital offering secondary care service to 350 000 patients. PATIENTS: Selected patients with an exacerbation of chronic obstructive pulmonary disease where hospital admission had been recommended after medical assessment. INTERVENTIONS: Nurse administered home care was provided as an alternative to inpatient admission. MAIN OUTCOME MEASURES: Readmission rates at two weeks and three months, changes in forced expiratory volume in one second (FEV_1) from baseline at these times and mortality. RESULTS: 583 patients with chronic obstructive pulmonary disease referred for admission were assessed. 192 met the criteria for home care, and 42 refused to enter the trial. 100 were randomised to home care and 50 to hospital care. On admission, FEV_1 after use of a bronchodilator was 36.1% (95% confidence interval 2.4% to 69.8%) predicted in home care and 35.1% (6.3% to 63. 9%) predicted in hospital care. No significant difference was found in FEV_1 after use of a bronchodilator at two weeks (42.6%, 3.4% to 81.8% versus 42.1%, 5.1% to 79.1%) or three months (41.5%, 8.2% to 74.8% versus 41.9%, 6.2% to 77.6%) between the groups. 37% of patients receiving home care and 34% receiving hospital care were readmitted at three months. No significant difference was found in mortality between the groups at three months (9% versus 8%). CONCLUSIONS: Hospital at home care is a practical alternative to emergency admission in selected patients with exacerbations of chronic obstructive pulmonary disease.

Early Percutaneous Tracheostomy After Median Sternotomy—Byhahn C, Rinne T, Halbig S, Albert S, Wilke HJ, Lischke V, Westphal K. J Thorac Cardiovasc Surg 2000 Aug;120(2):329-334.

OBJECTIVE: Tracheostomy offers significant advantages over endotracheal intubation in patients requiring long-term assisted ventilation. However, in patients who have undergone median sternotomy, it is believed that the danger of microbial contamination and consecutive infection of the sternal wound with microbes from the tracheostomy is high when conventional tracheostomy is performed. In contrast, percutaneous techniques are less likely to result in tracheostomy infection and thus bacterial contamination of neighboring structures. Nonetheless, to date there has been no prospective study confirming or disproving this assumption. Our study evaluated outcome after percutaneous tracheostomy in patients with a median sternotomy. METHODS: A total of 144 cardiac surgical patients had elective percutaneous tracheostomy at the bedside until postoperative day 14, with 4 different techniques. Systematic microbiologic monitoring of the sternal and tracheal wounds was used. RESULTS: In 13 patients sternal wound infection was suspected, but was confirmed in only 4 (2.8%) patients who actually showed microbial contamination of the sternum. In 2 of these patients, the identified microbes were not identical to those cultured from the trachea. The other 2 patients had sternal and tracheal cultures positive for methicillin-resistant Staphylococcus aureus. Cross-contamination of the sternotomy with microbes from the patient's airways was therefore ruled out. No patient had clinical signs of tracheostomy infection. Likewise, there were no cases of mediastinitis. CONCLUSIONS: On the basis of our data, we conclude that cross-contamination of the sternal wound with microbes from the trachea is not a problem. Elective percutaneous tracheostomy is safe, even if performed during the first 14 days after median sternotomy.

Are Patients at Veterans Affairs Medical Centers Sicker? A Comparative Analysis of Health Status and Medical Resource Use—Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Arch Intern Med 2000 Nov 27;160(21):3252-3257.

BACKGROUND: The Veterans Affairs (VA) health system has been criticized for being inefficient based on comparisons of VA care with

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non-VA care. Whether such comparisons are biased by differences between the VA patient population and the non-VA patient population is not known. Our objective is to determine if VA patients are different from non-VA patients in terms of health status and medical resource use. METHOD: We analyzed 128,099 records from the National Health Interview Survey for the years 1993 and 1994. We compared the VA patient population with the general patient population for self report on health status, number of medical conditions, number of outpatient physician visits, number of hospital admissions, and number of hospital days each year. RESULTS: The VA patient population had poorer health status (odds ratio [OR], 14.7; 95% confidence interval [CI], 10.7-20.2), more medical conditions (OR, 14; 95% CI, 10.5-18.7), and higher medical resource use compared with the general patient population (OR, 3.7 for 3 or more physician visits per year; OR 5.4 for 3 or more hospital admissions per year; OR, 7.7 for 21 or more days spent in a hospital per year). However, after controlling for health and sociodemographic differences, VA patients had similar resource use compared with the general patient population. CONCLUSION: Large differences in sociodemographic status, health status, and subsequent resource use exist between the VA and the general patient population. Therefore, comparisons of VA care with non-VA care need to take these differences into account. Furthermore, health care planning and resource allocation within the VA should not be based on data extrapolated from non-VA patient populations.

Clinical Signs and Symptoms Predicting Influenza Infection—Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Arch Intern Med 2000 Nov 27;160(21):3243-3247.

BACKGROUND: New antiviral drugs are available for the treatment of influenza type A and type B infections. In clinical practice, antiviral use has rarely been guided by antecedent laboratory diagnosis. Defined clinical predictors of an influenza infection can help guide timely therapy and avoid unnecessary antibiotic use. OBJECTIVE: To examine which clinical signs and symptoms are most predictive of influenza infection in patients with influenzalike illness using a large data set derived from clinical trials of zanamivir. METHODS: This analysis is a retrospective, pooled analysis of baseline signs and symptoms from phase 2 and 3 clinical trial participants. It was conducted in mainly unvaccinated (mean age, 35 years) adults and adolescents who had influenzalike illness, defined as having fever or feverishness plus at least 2 of the following influenzalike symptoms: headache, myalgia, cough, or sore throat who underwent laboratory testing for influenza. Clinical signs and symptoms were evaluated in statistical models to identify those best predicting laboratory confirmation of influenza. RESULTS: Of 3744 subjects enrolled with baseline influenzalike symptoms, and included in this analysis, 2470 (66%) were confirmed to have influenza. Individuals with influenza were more likely to have cough (93% vs 80%), fever (68% vs 40%), cough and fever together (64% vs 33%), and/or nasal congestion (91% vs 81%) than those without influenza. The best multivariate predictors of influenza infections were cough and fever with a positive predictive value of 79% ($p<0.001$). The positive predictive value rose with the increase in the temperature at the time of recruitment. CONCLUSION: When influenza is circulating within the community, patients with an influenzalike illness who have both cough and fever within 48 hours of symptom onset are likely to have influenza and the administration of influenza antiviral therapy may be appropriate to consider.

Impact of Zanamivir on Antibiotic Use for Respiratory Events Following Acute Influenza in Adolescents and Adults—Kaiser L, Keene ON, Hammond JM, Elliott M, Hayden FG. Arch Intern Med 2000 Nov 27;160(21):3234-3240.

BACKGROUND: Influenza infections commonly lead to respiratory tract complications that result in antibiotic treatment. OBJECTIVES: To determine frequency of respiratory events leading to antibiotic use following influenza illness in adolescents and adults, and to assess whether treatment with topical zanamivir prevents these complications. METHODS: Meta-analysis of 7 randomized, double-blind, placebo-controlled trials; 3815 mainly healthy adolescents and adults (mean age, 34 years) with an influenzalike illness of less than 2 days' duration were randomly assigned to receive combined inhaled and intranasal zanamivir, inhaled zanamivir, or corresponding placebos. Twelve percent of enrolled subjects were high-risk patients. The main outcome was the incidence of respiratory events leading to antibiotic prescriptions in patients with proven influenza. RESULTS: Influenza infections were laboratory confirmed in 2499 (66%) of 3815 patients (influenza A in 88% and B in 12%). Placebo recipients developed a respiratory event leading to antibiotic use in 17% of cases, mainly for acute bronchitis or acute sinusitis. Among zanamivir-treated patients (n = 1494) the incidence of respiratory events leading to the use of antimicrobials was 11% (relative risk [RR] compared with placebo, 0.69; 95% confidence interval [CI], 0.57-0.84). Intranasal and inhaled zanamivir seemed to reduce the number of upper (RR, 0.59; 95% CI, 0.36-0.97) and lower respiratory tract events (RR, 0.64; 95% CI, 0.38-1.08). Inhaled zanamivir reduced the number of lower respiratory tract events (RR, 0.60; 95% CI, 0.42-0.85), but the reduction in the number of upper respiratory tract events was not statistically significant (RR, 0.90; 95% CI, 0.63-1.27). CONCLUSIONS: Respiratory complications or worsening of symptoms leading to antibiotic use occurred in about 17% of adolescents or adults with influenza infection. Early treatment of influenza illness with zanamivir reduced the number of these antibiotic prescriptions.

Water Accumulation in Metered Dose Inhaler Spacers Under Normal Mechanical Ventilation Conditions—Waugh JB, Waugh JB. Heart Lung 2000 Nov-Dec;29(6):424-428.

OBJECTIVE: The purpose of this study was to compare the water accumulation in 3 types of metered dose inhaler (MDI) spacer shapes in-line in a ventilator circuit, in 2 positions over 2-, 4-, and 6-hour time periods through the use of heated- and nonheated-wire ventilator circuits. DESIGN: The study design was prospective, quasiexperimental, and random assignment. SETTING: The study was conducted in a university laboratory. MATERIALS: Three brands of MDI spacers (OptiVent, ACE, AeroVent) were tested. Outcome Measures: Grams of water accumulation were measured. INTERVENTION: Distilled water accumulation was measured in 3 brands of MDI spacers in 0 degrees and 45 degrees positions at 2-, 4-, and 6-hour time intervals. Water accumulation was measured in each spacer by calculating the differences between pretest (dry) weights and posttest (wet) weights through the use of an analytical balance. A Marquest SCT-3000 servo-controlled humidifier with heated-wire ventilator circuit was used with a room temperature range of 21.7 degrees C-22.8 degrees C (71 degrees -73 degrees F) and a relative humidity range of 57%-65%. RESULTS: Multivariate repeated measures analysis demonstrated a difference between brands ($p <0.001$). The amount of water accumulated during 6 hours (time variable) was significantly different ($p <0.001$), as was the interaction between time and "spacer brand" (with Greenhouse-Geisser adjustment). The interaction of time and position was also significantly different ($p =0.001$). Water accumulations at a 45 degrees angle were: AeroVent 0.765 $\pm$ 0.152 g; OptiVent 1.894 $\pm$ 0.228 g; and ACE 4.043 $\pm$ 0.665 g through 6 hours of use. CONCLUSIONS: We found that water accumulation was a result of the type of spacer, position of the spacer, and time that the spacer was left in-line. All 3 brands of spacer collected less than 5 mL of water over 6 hours in either position. Heated-wire circuits accumulated less water than nonheated-wire circuits and may be safer when using MDI spacers.

Women's Initiative for Nonsmoking (WINS) I: Design and Methods—Froelicher ES, Christopherson D. Heart Lung 2000 Nov-Dec;29(6):429-437.

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This article describes the design and methods of the Women's Initiative for Nonsmoking, a nurse-managed intervention for smoking cessation and relapse prevention in women hospitalized with cardiovascular disease. The Women's Initiative for Nonsmoking is a randomized clinical trial with a 3-month intervention period and follow-up at 6, 12, 24, and 30 months. Data were collected at 10 urban hospitals in the San Francisco Bay area. The sample consisted of 278 women, mean age 61 years, hospitalized with cardiovascular disease (angina, myocardial infarction, angioplasty, coronary artery bypass graft surgery, heart failure, valvular disease, peripheral vascular disease, and cerebrovascular disease). The behavioral intervention consisted of nurse-managed care focused on preventing relapse after smoking cessation during hospitalization. Measures included demographic, clinical (includes diagnosis and comorbidity data), smoking history, confidence questionnaire, stress, depression, and quality of life. This article provides a detailed description of research design and methods for researchers desiring to replicate the study and nurse practitioners developing a smoking cessation, risk-reduction program in the clinical setting. Results of the trial are forthcoming.

Women's Initiative for Nonsmoking (WINS) II: The Intervention— Martin K, Froelicher ES, Miller NH. Heart Lung 2000 Nov-Dec;29(6): 438-445.

Women's Initiative for Nonsmoking (WINS) is a randomized clinical trial designed to test the efficacy of a nurse-managed smoking cessation and relapse prevention intervention designed specifically for women. The WINS intervention is rooted in social learning theory, specifically that of self-efficacy. It is a multimedia approach that provides education, counseling, and telephone follow-up that meet the smoking cessation intervention guidelines established by the Agency for Health Care Policy and Research. The WINS intervention has been successfully implemented in more than 140 women and has proven to be feasible and well accepted by both the women and their health care providers. Although the intervention in the protocol-driven randomized clinical trial was begun in the hospital, it is anticipated that nurses in any setting, inpatient or outpatient, who serve populations at risk for cardiovascular disease, peripheral vascular disease, lung cancer, or pulmonary disease could successfully provide the intervention.

Augmentation Therapy Reduces Frequency of Lung Infections in Antitrypsin Deficiency: A New Hypothesis with Supporting Data— Lieberman J. Chest 2000 Nov;118(5):1480-1485.

STUDY OBJECTIVES: To propose an hypothesis that antiprotease augmentation therapy reduces the incidence of lung infections in α_1-antitrypsin (AAT)-deficient patients, and to present supporting data. DESIGN: The proposed concept is based on a survey taken via the Internet of patients receiving augmentation therapy for 1 to 10 years compared to similar patients not receiving such therapy. SETTING: A questionnaire was submitted to patients with a ZZ phenotype for AAT deficiency to determine whether those receiving antitrypsin augmentation therapy were aware of any personal benefit, and whether the therapy had an effect on the frequency of lung infections. PATIENTS: Ninety-six adult patients receiving human α_1-proteinase inhibitor (α_1-PI) responded, as did 47 similar patients not receiving augmentation therapy. RESULTS: Seventy-four of 89 patients who had received α_1-PI infusions for > 1 year believed that they had definitely benefited from such therapy. Fifty-six of the 74 patients claiming a benefit attributed this to a reduction in the number of lung infections since starting therapy with α_1-PI infusions. Before starting α_1-PI, the majority of patients had three to five infections per year, dropping to zero to one infection per year during α_1-PI therapy ($p < 0.001$). CONCLUSIONS: Replacement therapy for AAT deficiency-associated emphysema appears to be associated with a marked reduction in the frequency and severity of lung infections. This association must be evaluated further in future, more rigid, prospective studies of AAT augmentation therapy. Findings support the hypothesis that antiprotease therapy with α_1-PI reduces the incidence of lung infections in addition to slowing the deterioration of lung function and causing a reduction in mortality.

Preoperative Severity of Emphysema Predictive of Improvement After Lung Volume Reduction Surgery: Use of CT Morphometry— Rogers RM, Coxson HO, Sciurba FC, Keenan RJ, Whittall KP, Hogg JC. Chest 2000 Nov;118(5):1240-1247.

STUDY OBJECTIVES: To determine how the volume and severity of emphysema measured by CT morphometry (CTM) before and after lung volume reduction surgery (LVRS) relates to the functional status of patients after LVRS. DESIGN: A histologically validated CT algorithm was used to quantify the volume and severity of emphysema in 35 patients before and after LVRS: total lung volume (TLV), normal lung volume (< 6.0 mL gas per gram of tissue), volume of mild/moderate emphysema (ME; 6.0 to 10.2 mL gas per gram of tissue), volume of severe emphysema (> 10.2 mL gas per gram of tissue), surface area/volume (SA/V; meters squared per milliliter), and surface area (SA; meters squared). Outcome parameters included maximal cardiopulmonary exercise (CPX) performance in 21 patients and routine pulmonary function in all patients. We hypothesized that baseline CTM parameters predict response to LVRS and that the change in these parameters may offer insight into mechanisms of improvement. Patients and intervention: Thirty-five patients with severe emphysema who had successful LVRS. RESULTS: The significant decrease in TLV following LVRS was entirely accounted for by a decrease in severe emphysema. The SA/V and the SA both increased significantly following LVRS. The change in maximal CPX in watts following surgery correlated significantly with baseline values of severe emphysema ($r = 0.60$), which was collinear with TLV, and SA/V. The change in diffusing capacity of the lung for carbon monoxide revealed a significant positive linear relationship with preoperative severe emphysema ($r = 0.37$) and a negative relationship with ME ($r = -0.37$). Change in watts revealed a strong relationship with changes in severe emphysema ($r = -0.75$) and weaker but significant relationships with change in TLV, ME, SA/V, and SA. Other measures of pulmonary function revealed significant albeit less dominant relationships with baseline CTM and change in these indexes. CONCLUSION: Using CTM, we have identified a close relationship between baseline severe emphysema, or change in severe emphysema, and the improvement in CPX after LVRS. These observations support a potential role of CTM in future clinical trials for predicting responders to LVRS and identifying mechanisms of improvement.

Acid-Base Disturbance

Patient care providers are frequently confronted with acid-base disturbances. These can range from a simple respiratory acidosis or alkalosis, metabolic acidosis or alkalosis, to a more complex mixed acid-base disorder. In general, acid-base disturbances are manifestations or complications of a pre-existing disease. In fact, they may prompt us to serious conditions that require immediate attention.

Two major organs are involved in maintaining acid-base homeostasis: the lungs and the kidneys. Both function collectively to achieve that common goal. Hence, in this special issue on acid-base disorders, to cover a comprehensive area from basic science physiology to clinical application, we have solicited recognized authors from both nephrology and pulmonary medicine who have special interest in acid-base regulation.

The understanding of acids and bases originated in 1834 when an English physicist, Michael Faraday, discovered that acids, bases, and salts are electrolytes.[1] In 1884 Svante Arrhenius, a Swedish chemist, proposed that an acid is defined as a hydrogen-containing compound that, when dissolved in water, produces a concentration of hydrogen ions (H^+).[2] Similarly, a base is defined as a substance that, when dissolved in water, produces an excess of hydroxide ions (OH^-). Since then, scientists have further refined our understanding of acid-base and have been able to measure the strength of an acid, known as pH, that is, the negative logarithm of H^+ activity of a solution. Like other topics in medicine, knowledge in acid-base disorders continues to evolve, and this special issue attempts to keep the readers abreast of current developments in this area.

In acid-base disorders, knowledge of normal acid-base balance is closely linked to understanding its disturbance. Virtually all disturbances of acid-base regulation are examples of pure pathophysiology. It would be difficult to understand the pathophysiology of a specific disturbance without an understanding of the normal acid-base homeostasis. Accordingly, this issue begins with a discussion of how the body maintains acid-base homeostasis, followed by specific acid-base disturbances, and concludes with the general clinical approach to patients with acid-base disorders. We hope that the readers of Respiratory Care find this special issue informative and up-to-date.

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Acid-Base Physiology

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Acid-base homeostasis involves chemical and physiologic processes responsible for the maintenance of the acidity of body fluids at levels that allow optimal function of the whole individual. The chemical processes represent the first line of defense to an acid or alkali load and include the extracellular and intracellular buffers, whereas the physiologic processes modulate acid-base composition by changes in cellular metabolism and by adaptive responses in the excretion of volatile acids by the lungs and fixed acids by the kidneys. The need for the existence of multiple mechanisms involved in acid-base regulation stems from the critical importance of the hydrogen ion (H^+) concentration on the operation of many cellular enzymes and function of vital organs, most prominently the brain and the heart. The task imposed on the mechanisms that maintain acid-base homeostasis is large, since metabolic pathways are continuously consuming or producing H^+, and the daily load of waste products for excretion in the form of volatile and fixed acids is substantial. We review the determinants of the acidity of body fluids, the mechanisms that maintain normal acid-base composition, and the overall defense to disruption in acid-base equilibrium. Specific topics include an examination of the scales of acidity, buffer systems, intracellular acid-base regulation, excretion of acids, alkali and acid loading, and normal acid-base composition. The limitations of arterial blood sampling in the assessment of acid-base status are also evaluated. *Key words: acid-base physiology, acid-base regulation, buffer systems, arterial blood sampling, alkali loading, acid loading.* [Respir Care 2001;46(4):328–341]

Introduction

Maintenance of acid-base homeostasis is a vital function of the living organism, largely because of the effects of acidity on body proteins. Chemical and physiologic processes are responsible for the stability of the acid-base status of intracellular fluids (ie, pH 7.00–7.30, depending on the cell and tissue of origin) and extracellular fluids (ie, pH 7.35–7.45) at levels that allow optimal function of the

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whole individual.[1,2] The chemical processes represent the first line of defense to an acid or alkali load and include the extracellular and intracellular buffers. The physiologic processes modulate acid-base composition by changes in cellular metabolism and by adaptive responses in the excretion of volatile acids by the lungs and fixed acids by the kidneys.[3] The need for the existence of multiple mechanisms involved in acid-base regulation stems from the critical importance of the hydrogen ion (H^+) concentration on the operation of many cellular enzymes and on the function of vital organs, most prominently the brain and the heart. The task imposed on the processes and organs that maintain acid-base homeostasis is large, since metabolic pathways are continuously consuming or producing H^+, and the daily load of waste products for excretion in the form of volatile and fixed acids is substantial.

Scales of Acidity: pH versus Nanomoles per Liter

Acidity of body fluids may be expressed as a molar concentration such as nanomoles per liter (nmol/L or 10^{-9} mol/L) or as a pH value, the latter being the negative logarithm of H^+ activity of a solution in which the concentration of H^+ ($[H^+]$) is expressed in mol/L. However, measurement of acidity is always performed by means of a glass pH electrode[4] that allows protons (H^+) but not other ions to diffuse through it. The glass of the electrode is interposed between the sample and a known buffer solution. The proton gradient between the sample and the buffer solution creates an electrical potential that is measured and the magnitude of which is proportional to the proton gradient and, thus, dependent on the $[H^+]$ in the sample. The pH electrode measures the H^+ "activity" but not the H^+ concentration. In an ideal diluted solution the lack of substantial interaction between ions results in a ratio between "activity" and concentration equal to one. Since the $[H^+]$ in most body fluids is very low (ie, the behavior of H^+ resembles that found in an ideal solution), it is appropriate to equate activity to concentration of H^+. The major difference between expressing the acidity of a solution in nmol/L and pH units is that the former uses an arithmetic scale, whereas the pH notation is a logarithmic scale. Thus, when acidity is expressed in pH units, because of the logarithmic scale conceptualization of quantitative changes in acidity can become difficult. For example, a change in pH from 7.40 to 7.10 represents an increase in $[H^+]$ from 40 nmol/L to 80 nmol/L (ie, 100% increase).

Three methods can be used to make the conversion between the two scales.[2] The first method, which is the most precise, is as follows: in order to convert pH values to $[H^+]$ in nmol/L (nEq/L), the pH value must first be subtracted from 9.00 and its antilog subsequently obtained. The reverse, to convert $[H^+]$ in nmol/L to pH, is accomplished by obtaining first the log of the nmol/L and then subtracting it from 9.00. The rationale for subtracting from 9.00 when expressing acidity in nmol/L is that pH 9.00 represents the start of the scale and amounts to 1 nmol/L (10^{-9} mol/L). For example, the $[H^+]$ for a pH of 7.15 is calculated as follows: we must first subtract 7.15 from 9.00, which is 1.85; then we should obtain the antilog of 1.85, which is 71; thus a pH of 7.15 is equivalent to a $[H^+]$ of 71 nmol/L.

A second method is to apply the rule whereby for each 0.01 pH unit below or above its normal value, 1 nmol/L is respectively added or subtracted. Since a pH of 7.40 is equal to 40 nmol/L (nEq/L) of $[H^+]$, pH values of 7.50 and 7.30 correspond to $[H^+]$ of 30 and 50 nmol/L, respectively. This rule is relatively accurate for a limited range of pH, of about 0.2 pH units below and above the normal value (7.20 to 7.60). It must be recognized, however, that this rule is inaccurate for extreme deviations of pH, and therefore should not be used in those circumstances.

A third method of converting pH values to $[H^+]$ in nmol/L is the 80% method (or 0.8 method), which is useful for any blood pH value and does not require a calculator with a logarithmic capability. This method requires remembering that a pH of 7.40 and a pH of 7.00 correspond to $[H^+]$ of 40 nmol/L and 100 nmol/L, respectively. For an increase in pH equal to 0.10 units starting from a selected pH value, one must multiply the $[H^+]$ by 0.8. For example, the $[H^+]$ for a pH of 7.10 and a pH of 7.20 are 80 nmol/L and 64 nmol/L, respectively. These values are obtained by multiplying 0.8×100 nmol/L ($[H^+]$ for a pH of 7.00) for the former, and $0.8 \times 0.8 \times 100$ nmol/L for the latter. The 80% method is reliable and has practical value.

Buffer Systems

The relative stability of the pH of body fluids, despite the continuous production of sizeable quantities of acid by metabolism, in health and disease, is fully dependent on the presence of large amounts of body buffers.[4] A buffer is a compound that ameliorates the change in acidity that would otherwise occur in response to the addition of acid or alkali to a solution. Body buffers include the carbonic acid-bicarbonate system and non-HCO_3^- buffers (eg, proteins, phosphate).

The relative strength of a buffer system in the defense of pH is quantified by the so-called buffer value. The buffer value of a solution is the amount of acid or alkali required to alter the acidity of a solution by 1 pH unit. It is expressed in units called slykes (sl) (in honor of Donald D Van Slyke, U.S. biochemist, 1883–1971), which are equivalent to mEq/L/pH unit.[2] When the bicarbonate buffer system is compared with the non-HCO_3^- buffer system in terms of buffer value, a substantial difference in the strength of buffer action is found. The buffer value of HCO_3^- is 2.3

sl/mmol, whereas that of HPO_4^{2-} is only 0.58 sl/mmol: thus, the molar buffer value of HCO_3^- is 4 times that of ordinary buffers like HPO_4^{2-}. The mechanism responsible for the 4-fold larger buffer value of bicarbonate is the disappearance of the acid (as carbon dioxide gas) resulting from acid titration of HCO_3^-, which occurs only with the H_2CO_3/HCO_3^- system and not with ordinary buffers, since the acid form of the buffer pair of ordinary buffers remains in solution.

The effects of an acid or alkali load derived from any source will alter the composition of the various body buffers, which will subsequently interact with each other according to the isohydric principle.[4] This postulate dictates that the acid/base ratio of all the different buffer pairs present in body fluids (such as H_2CO_3/HCO_3^-, $H_2PO_4^-/HPO_4^{2-}$, protein H^+/protein$^-$) is altered in a predictable manner in response to a change in the $[H^+]$ of these fluids. The law of mass action is defined by the following formula for the case of $[H^+]$:

$$[H^+] = K_2 \frac{[HA]}{[A^-]} \quad (1)$$

wherein A^- is a base and HA is a weak acid. If several buffers are in solution, the relationships among the buffer pairs are as follows:

$$[H^+] = K_{a1} \frac{[H_2CO_3]}{[HCO_3^-]} = K_{a2} \frac{[H_2PO_4^-]}{[HPO_4^{2-}]} = K_{a3} \frac{[\text{Protein } H^+]}{[\text{Protein}^-]} \quad (2)$$

where K_{a1}, K_{a2}, and K_{a3} are the respective dissociation constants for each buffer pair. Since the buffer pair quantified in clinical practice to assess acid-base status is the H_2CO_3/HCO_3^-, we use the following formula, known as the Henderson equation:

$$[H^+] = 24 \times \frac{P_{CO_2}}{HCO_3} \quad (3)$$

In this equation, the $[H^+]$ is expressed in nmol/L, partial pressure of carbon dioxide (P_{CO_2}) in mm Hg, and $[HCO_3^-]$ in mmol/L. To obtain hydrogen ion activity as pH, the Henderson equation is modified by taking the negative logarithm of each side, as follows:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \times P_{CO_2}} \quad (4)$$

This is the Henderson-Hasselbalch equation, which uses the same units for P_{CO_2} and $[HCO_3^-]$ as the Henderson equation.

The physiologic control of $[H^+]$ in humans is not exerted by a direct effect on the pH of body fluids.[1,2] Instead, acidity is modulated by altering the levels of the components that determine $[H^+]$, namely P_{CO_2} and bicarbonate concentration; whereas P_{CO_2} is regulated by the lungs, the plasma bicarbonate concentration ($[HCO_3^-]_p$) is largely regulated by the kidneys. It must be recognized that the level of P_{CO_2} in body fluids is determined by the relationship between CO_2 production by the tissues and its excretion by the lungs. The lungs excrete the CO_2 produced from tissue metabolism, which is present in body fluids as dissolved CO_2 and carbonic acid. Thus, CO_2 excretion by the lungs maintains a constant P_{CO_2} in arterial blood and thereby limits the accumulation of carbonic acid. With respect to the concentration of bicarbonate in body fluids, its steady-state value results from ongoing processes that decompose HCO_3^-, counterbalanced by other processes that regenerate it. The major component of bicarbonate decomposition is the release of fixed acids derived from cellular metabolism, whereas regeneration of bicarbonate stores is accomplished by proton-consuming metabolic pathways and the excretion of acid by the kidneys.

A load of fixed acids (as opposed to the volatile carbonic acid) titrates the bicarbonate and the non-HCO_3^- buffer systems of all body compartments, including the intracellular and extracellular fluids. Although the buffer value of fluids within and outside cells is approximately equal when expressed per liter (approximately 64 slykes), the greater amount of intracellular fluid, in comparison with the extracellular fluid (ratio is 1.5:1), accounts for the greater contribution of the intracellular buffers. It should be recognized, however, that the fractional contribution of bicarbonate and non-HCO_3^- buffers in each fluid is substantially different. Whereas HCO_3^- accounts for approximately 36% of the intracellular fluid buffer value, the non-HCO_3^- buffers (eg, proteins, HPO_4^{2-}) account for approximately 64% of this value. The contribution of HCO_3^- to the buffer value of extracellular fluid is very large, amounting to approximately 86%, and the remainder, approximately 14%, is from non-HCO_3^- buffers. Thus, the fractional contribution of the two buffer systems differs substantially in extracellular fluid with respect to intracellular fluid.[1,2]

In contrast with the response to a load of fixed acids, which titrates the bicarbonate as well as the non-HCO_3^- buffer systems, the volatile carbonic acid challenges exclusively the non-HCO_3^- buffer system.[2,5–7] Thus, the non-HCO_3^- buffer system can be precisely assessed by titration with CO_2 gas as follows:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (5)$$

$$HCO_3^- + H^+ + Buf^- \leftrightarrow HBuf + HCO_3^- \quad (6)$$

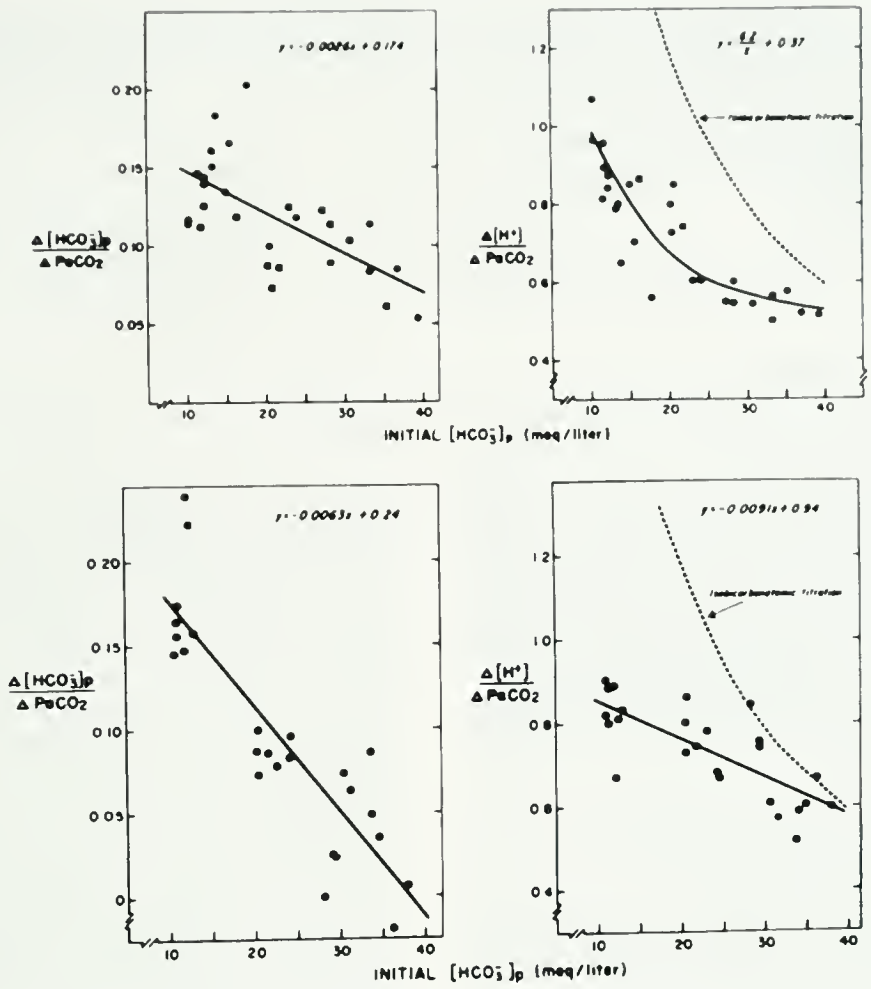

Fig. 1. Relationship between initial level of plasma bicarbonate concentration ($[HCO_3^-]_p$) and slope of $[HCO_3^-]_p$/arterial partial pressure of carbon dioxide (P_{aCO_2}) regression line ($\Delta[HCO_3^-]_p/\Delta P_{aCO_2}$, left) or slope of hydrogen ion concentration ($[H^+]$)/P_{aCO_2} regression line ($\Delta[H^+]/\Delta P_{aCO_2}$, right) for all acute carbon dioxide titration studies in dogs with chronic metabolic (upper panel) or chronic respiratory (lower panel) acid-base disturbances. Although the buffering response of animals with an initial low $[HCO_3^-]_p$ (independently of whether it resulted from either a chronic metabolic or a respiratory disturbance) was greater than those with an initial high $[HCO_3^-]_p$, the observed change in pH was larger in the former group because of the mathematical constraints of the Henderson equation. (From References 6 and 7, with permission.)

In this reaction the newly generated H^+ resulting from the dissociation of H_2CO_3 is picked up by non-HCO_3^- buffers. The amount of HCO_3^- generated during the CO_2 titration is identical to the amount of H^+ removed from the body fluids by the non-HCO_3^- buffers. Therefore, the change in $[HCO_3^-]_p$ per unit change in P_{CO_2} ($\Delta[HCO_3^-]_p/\Delta P_{CO_2}$) or per unit change in blood pH ($\Delta[HCO_3^-]_p/\Delta pH$) quantifies the buffering response of non-HCO_3^- buffers (Fig. 1). Of great interest is the observation that the buffering response of animals with an initial low $[HCO_3^-]_p$ (independently of whether it resulted from either a chronic metabolic disturbance or a respiratory disturbance) was greater than those with an initial high $[HCO_3^-]_p$. However, despite the more intense buffering defense, the observed change in blood pH was larger in animals with low $[HCO_3^-]_p$ because of the mathematical constraints of the Henderson equation. Consequently, the presence of a high plasma bicarbonate results in a better protection in terms of a smaller change in pH during acute hypercapnia, in spite of a more limited buffering response.

Among the major buffer systems involved in the in vivo response to an acid load, in addition to those reviewed above, are the bone carbonates.[8] This reserve of alkali stored in the skeleton amounts to a total of approximately 35,000 mEq in an adult and contributes substantially to the buffering capacity of the body. It has been estimated that

Table 1. Overview of H^+-Producing and H^+-Consuming Pathways in the Metabolism of Carbohydrates, Fats, and Proteins (ie, Amino Acids)

	H^+-Producing Pathways	H^+-Consuming Pathways
Carbohydrates	Glucose → 2 Lactate + 2 H^+	2 Lactate + 2 H^+ → Glucose
	Lactate + NAD^+ → Pyruvate + NADH + H^+	2 Lactate + 2 H^+ + 6 O_2 → 6 CO_2 + 6 H_2O
Fat stores	Triglyceride → 3 Fatty acid anions + 3 H^+	3 Fatty acid anions + 3 H^+ → Triglyceride
	Palmitate + 6 O_2 → 4 Ketone anions + 3 H^+ + 2 H_2O	4 Ketone anions + 3 H^+ + 2 H_2O → Palmitate
		Ketone anions + H^+ → CO_2 + H_2O
Proteins	2 NH_4^+ + CO_2 → Urea + 2 H^+ + H_2O (neutral amino acids: 1 NH_4^+; dicarboxylic amino acids: 1 NH_4^+; basic amino acids: 2 NH_4^+)	Amino acids → HCO_3^- (neutral amino acids: 1 HCO_3^-; dicarboxylic amino acids: 2 HCO_3^-; basic amino acids: 1 HCO_3^-)

NAD^+ = oxidized nicotinamide adenine dinucleotide
NADH = reduced nicotinamide adenine dinucleotide

about 40% of the buffering of an acute acid load occurs in the bones. The proton acceptance by the skeleton is accompanied by the release of Ca^{2+} or Na^+. Alternatively, HPO_4^{2-} uptake by bone tissues from the extracellular fluid may accompany the H^+ acceptance. Patients with chronic metabolic acidosis, especially in the presence of chronic renal failure, develop a major depletion of skeleton mineral content that is partly the result of buffering of H^+ by bone carbonates.

Generation, Consumption, and Excretion of Hydrogen Ions

The major source of hydrogen ions in the living organism is the reversible reaction of hydrolysis of cellular adenosine triphosphate (ATP), as follows:

$$ATP^{4-} + H_2O \leftarrow ADP^{3-} + H^+ + HPO_4^{2-} \quad (6)$$

where ADP = adenosine 5′-disphosphate. In turn, the sources of ATP are the oxidative degradation of carbohydrates, fats, and proteins, as explained below. In addition, the equilibrium reaction of water and CO_2, the end product of oxidative metabolism, results in the daily formation of large amounts of carbonic acid.

The daily production of fixed acids, commonly referred to as "endogenous acid production," is approximately 70–100 mEq/d (approximately 1.0–1.5 mEq of H^+/kg body wt/d) and is removed from body fluids by the kidney, according to the classic interpretation.[9] Consequently, the daily production of volatile acid, approximately 15,000 mEq/d, is approximately 200-fold that of fixed acids and explains the development of severe acidemia because of CO_2 retention within minutes of a respiratory arrest, whereas it takes days to reach a comparable deviation of acidity as a result of retention of fixed acids in the absence of renal function. The endogenous acid production is mostly composed of waste products and other substances derived from the intermediate metabolism of energy-rich compounds. The relatively small net daily production of acids in the normal state occurs in the presence of a large proton generation and proton consumption in major metabolic pathways of carbohydrates, lipids, and proteins.[1]

Glycolysis is the proton-producing pathway from carbohydrates, leading to the synthesis of lactic or pyruvic acids. Conversely, regeneration of glucose from lactic acid or complete oxidation of the latter to CO_2 and water consumes hydrogen ions (Table 1). It has been estimated that approximately 1,300 mmol of lactate and H^+ enter the circulation in a resting 70 kg subject every 24 hours, and an almost identical amount of this organic acid is removed by the tissues, mostly the liver. A large imbalance between synthesis and consumption of lactic acid is responsible for the development of various forms of lactic acidosis.

Lipolysis in peripheral tissues produces fatty acids, which in turn can undergo partial oxidation, leading to the formation of ketoacids. Proton production through these pathways amounts to about 300 mmol/d in normal individuals, and an almost identical quantity of these acids is consumed with the synthesis of triglyceride and fatty acids (see Table 1). However, a large imbalance between degradation and synthesis of body fats is observed in states of diabetic, alcoholic, or starving ketoacidosis. In alcoholic ketoacidosis, a condition that reflects an abnormal fatty acid oxidation with low caloric intake or recurrent vomiting, serum lactate is also commonly increased.

Disposal of ammonium (NH_4^+) during oxidation of amino acids in an individual with 100 g of dietary protein intake generates approximately 1,000 mmol/d of H^+ by the liver in the process of urea synthesis. However, an identical H^+ load is consumed in body tissues, with complete oxidation of the carbon skeletons of amino acids if the protein entirely consists of neutral amino acids. During oxidation, dicarboxylic amino acids (glutamate and aspartate) generate 2 HCO_3^- for each NH_4^+, whereas basic

Table 2. Effects and Consequences of Acidemia on H^+ Producing Pathways from Oxidation of Protein (ie, Amino Acids)

Direct Effect		Indirect Effect		Consequences
Kidney:	Increases urinary NH_4^+ excretion	→ Liver	Reduces supply of NH_4^+ for urea synthesis	→ Alkalinizing effect secondary to decreased H^+ production
			↑	
Liver:	Alters nitrogen disposal pathways Augments glutamine synthesis delivering substrate to kidney Decreases urea synthesis	→ Kidney	Increased urinary NH_4^+ excretion	→ Alkalizing effect secondary to decreased H^+ production

amino acids (eg, lysine) generate 2 NH_4^+ for each HCO_3^- (see Table 1). Excess protons are also produced during degradation of sulfur-containing amino acids by the oxidation of sulfur. In well-fed subjects the type of proteins in the diet largely account for differences in the net daily production of fixed acids. Conversely, in starved subjects the utilization of endogenous proteins determines the net acid production from this energy source. An imbalance between the proton load generated by urea synthesis and the bicarbonate production from oxidation of the carbon skeletons of amino acids can lead to a deviation of the normal acid-base status. Furthermore, states of abnormal acid-base composition have a major influence on proton generation and consumption in major metabolic pathways, as described below.

Acidemia of both metabolic and respiratory origin inhibits glycolysis, whereas alkalemia stimulates it.[10,11] This effect is mediated, at least in part, by the pH-sensitive enzyme phosphofructokinase, that plays a key rate-limiting role in glycolysis. Acidemia also stimulates renal lactate utilization, but inhibits hepatic lactate utilization. In addition, acid-base balance alters ketoacid metabolism in a manner comparable to that of lactic acid.[12] A low systemic pH inhibits ketoacid production, whereas a high pH stimulates it. Consequently, there is a pH feedback control of endogenous acid production. Under conditions of excessive lactic or ketoacid production, the resultant acidemia feeds back to inhibit the rate of endogenous acid production, thereby serving as a protective mechanism. Similarly, amino acid oxidation is substantially altered in response to changes in systemic acidity. Hepatic urea synthesis and its associated proton generation (2 H^+ are generated per molecule of urea synthesized) are inhibited by a low systemic pH. Conversely, alkalemia stimulates urea synthesis and therefore leads to increased proton generation, facilitating correction of the altered systemic acidity. Acidemia also has a direct effect on the kidney, which increases urinary NH_4^+ excretion, thereby facilitating nitrogen disposal and promoting proton excretion. Table 2 provides a synopsis of the direct and indirect effects of acidemia on the liver and kidney.

Intracellular Acid-Base Regulation

The mechanisms responsible for maintaining optimal intracellular acidity include buffering (largely by cellular proteins), modulation of the rate of ATP hydrolysis, and disposal of hydrogen ions into the extracellular fluid. The first two mechanisms have been briefly reviewed in the previous sections.

Evaluation of the cellular disposal of protons toward the extracellular fluid requires consideration of the transmembrane gradient of hydrogen ions.[2,13] The Nernst equation establishes that if a negative cell interior of 58 mV (resting membrane potential) and an extracellular pH of 7.40 (ie, 40 nmol/L) are present, the intracellular hydrogen concentration should be 10-fold higher (ie, 400 nmol/L or pH 6.40) to satisfy electrochemical equilibrium (passive diffusion of protons across the cell membrane).[2] Considering that the resting membrane potential of many cells is higher than –58 mV (eg, –80 mV), the expected cell acidity should be even lower than pH 6.40. Since cellular pH is 7.00 or higher, the cells must have active mechanisms for proton extrusion that account for the distribution of hydrogen ions above electrochemical equilibrium. The membrane-bound Na^+–H^+ antiporter, a mechanism of proton extrusion present in many cells, uses the energy derived from the electrochemical gradient for sodium across the membrane, which favors movement of sodium into the cell, for active extrusion of protons.

Changes in cellular metabolism that either accelerate or retard the production of fixed acids in response to changes in systemic pH are also important for acid-base homeostasis, as previously mentioned. Alkalemia stimulates, whereas acidemia inhibits, the production of organic acids such as lactic and ketoacids. Thus, the tissue metabolic response appears to be aimed at preserving the normalcy of acid-base equilibrium. In addition, urea production is inhibited by acidemia and this response appears to be homeostatic in nature, since ureagenesis consumes bicarbonate ions. Alterations in intracellular acidity activate one or more of the various mechanisms that facilitate the relative constancy of cell pH.

Pulmonary Excretion of Volatile Acid

In normal individuals maintaining a relatively uniform level of activity and stable diet, the daily rate of CO_2 production is remarkably constant. During maximal exercise, CO_2 production increases by as much as 20-fold, but the associated hyperventilation keeps the CO_2 tension in body fluids relatively constant.[14] In addition, diets very rich in carbohydrates yield greater amounts of CO_2, and that effect might have clinical implications in patients with respiratory failure or those with limited ventilatory reserve.

The uninterrupted flow of blood continuously transports the CO_2 produced by the tissues to the lungs for excretion to the atmosphere. Most of the CO_2 entering the circulation is converted to nongaseous forms for transport by mechanisms that depend largely on certain properties of hemoglobin, a critically important non-HCO_3^- buffer.[15] Yet the process of diffusion is the fundamental driving force responsible for the steady flow of CO_2 from the tissues to the blood and from the blood to the alveolar spaces of the lungs. Decomposition of carbonic acid produced in the tissues releases H^+, which is buffered by hemoglobin, and the CO_2 is converted to other molecular forms in the blood stream, including bicarbonate ions and carbamino compounds.[16–19] Because of the efficiency with which gaseous CO_2 is transported in the blood from tissues to lungs, a remarkably small gradient for P_{CO_2}, of only about 6 mm Hg, is required (since mean tissue P_{CO_2} and alveolar P_{CO_2} are approximately 46 mm Hg and 40 mm Hg, respectively). If transport of CO_2 occurred exclusively as physically dissolved gaseous CO_2 in plasma, a partial pressure gradient of CO_2 between tissues and lungs greater than 10 times the normal value would be required to secure excretion of daily CO_2 load.

The quantity of CO_2 absorbed by whole blood is a direct function of P_{CO_2} level. In addition, at any given P_{CO_2}, more CO_2 can be carried by reduced blood than by oxygenated blood; this phenomenon is referred to as the Haldane effect. Conversely, adding CO_2 or hydrogen ions to blood decreases the oxygen-binding affinity of hemoglobin, a phenomenon known as the Bohr effect. The interactions between the Haldane and Bohr effects promote optimal transport of both oxygen and CO_2, enlarging the difference in oxygen content between arterial and venous blood and reducing the arteriovenous P_{CO_2} gradient (Fig. 2). It is estimated that these interactions account for up to 40% of the tissue CO_2 unloading and 20% of tissue O_2 uptake.

The bulk of CO_2 transported to the lungs for excretion is carried in the form of bicarbonate ions. The higher $[HCO_3^-]$ in venous blood than in arterial blood is precisely due to the CO_2 released from the tissues and added to the

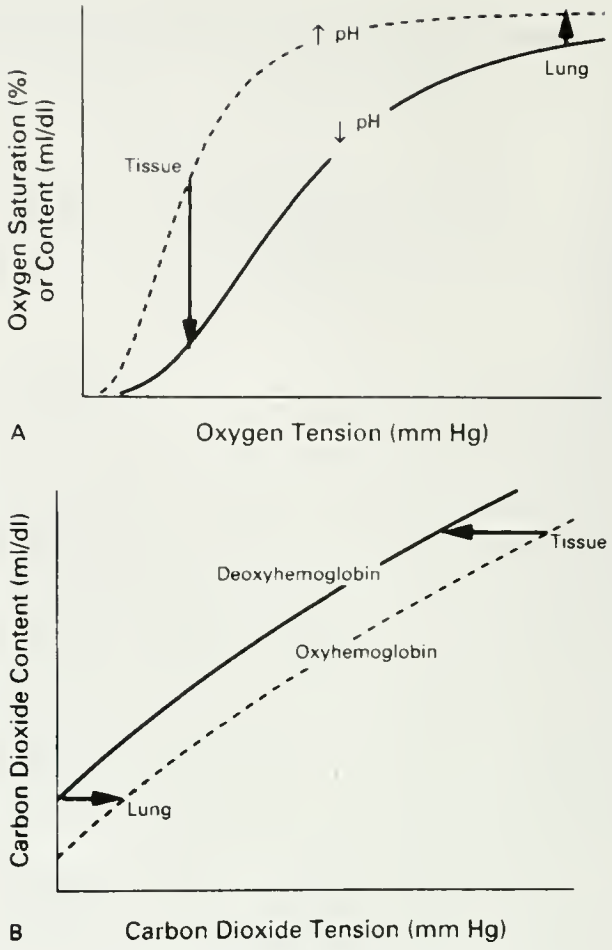

Fig. 2. Physiologic changes in oxygen and carbon dioxide binding to hemoglobin. The upper panel depicts the Bohr effect, which maximizes the difference in arteriovenous oxygen content as a result of changes in the binding affinity of hemoglobin for oxygen; these changes are caused by the uptake or release of carbon dioxide in peripheral tissues and lungs, respectively. The lower panel depicts the Haldane effect, which minimizes the difference in arteriovenous CO_2 tension as a result of changes in the binding affinity of hemoglobin for CO_2; these changes are caused by the uptake or release of oxygen in lungs and tissues, respectively. (From Hsia CCW. Respiratory function of hemoglobin. N Engl J Med 1998;338(4):239–247, with permission.)

blood for excretion to the atmosphere. Venous blood $[HCO_3^-]$ is about 2 mEq/L (mmol/L) higher than the arterial value, and this arteriovenous $[HCO_3^-]$ difference may be used to estimate the daily rate of carbonic acid production. The product of the arteriovenous difference of $[HCO_3^-]$/L of blood and the cardiac output in liters per minute yields the CO_2 production in mmol/L. This value multiplied by 1,440 minutes (per day) provides the daily CO_2 production in mmol. Thus, 2 mEq/L × 5 L/min of cardiac output × 1,440 min/d = 14,400 mEq/d (approximately 15,000 mEq/d carbonic acid production). As CO_2 diffuses from tissues to venous blood, it passes freely into

red cells, where it is rapidly hydrated under the catalytic influence of carbonic anhydrase to form carbonic acid:

$$CO_2 + H_2O \xleftrightarrow[\text{anhydrase}]{\text{carbonic}} H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (7)$$

As carbonic acid concentration rises, hemoglobin is titrated and thereby generates bicarbonate ions. The buffering ability of hemoglobin is greatly enhanced by the reduced oxygen tension prevailing in venous blood, because the dissociation constant (pK') of reduced hemoglobin is higher than that of oxyhemoglobin. A lesser but substantial portion of the CO_2 entering the erythrocyte combines directly and reversibly with certain amino groups of the hemoglobin molecule to form carbamino compounds.

The entire sequence of events that result in the transfer of CO_2 from the tissues to the blood stream is reversed in the pulmonary capillaries. Because the CO_2 tension in the alveolar atmosphere is lower than that in the blood compartment (ie, 40 mm Hg and 46 mm Hg, respectively), the prevailing CO_2 pressure gradient allows for the unloading of CO_2. The reduction in P_{CO_2} of the blood perfusing the pulmonary alveoli results in local alkalemia that challenges hemoglobin and other non-HCO_3^- buffers of the blood. Thus, these compounds release hydrogen ions that titrate both intraerythrocytic and plasma bicarbonate ions, producing carbonic acid. Because oxygenation of hemoglobin transforms this compound into a stronger acid, the release of hydrogen ions by hemoglobin is further enhanced. The newly generated carbonic acid is rapidly dehydrated by red blood cell carbonic anhydrase and by carbonic anhydrase located on the endothelial surface of the alveolar capillaries.[20,21] In fact, the carbonic anhydrase of the pulmonary capillaries has been shown to increase the efficiency of CO_2 transfer across the alveolar-capillary membrane.[22–24] Consequently, inhibition of carbonic anhydrase of red cell and lung can produce respiratory acidosis. Carbonic anhydrase is also found in the epithelium of the small airways and participates in the actions of CO_2 on bronchial tone. The concept of direct effects of CO_2 on airway resistance, including hypocapnic bronchoconstriction and hypercapnic bronchodilation, is well established and presumably involves carbonic anhydrase-catalyzed changes in local H^+ concentration. Furthermore, if has been proposed that carbonic anhydrase located in the airway epithelium participates in matching alveolar ventilation to the respective level of capillary perfusion in different lung regions.[20,25] Carbamino CO_2 is also released for excretion. The high permeability of the alveolar capillary membrane to CO_2 (about 20 times greater than that to O_2) allows for the rapid equilibration of the CO_2 tension between blood and alveolar compartments, which occurs within a fraction of the transit time of the red blood cells along the pulmonary capillaries.

Alveolar ventilation (ie, the volume of fresh inspired gas entering the alveoli) is inversely related to arterial P_{CO_2}, as follows:

$$P_{aCO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \quad (8)$$

where $\dot{V}_{CO_2}$ is the volume of CO_2 expired per unit of time, ($\dot{V}_A$) is alveolar ventilation, and K is a constant. Consequently, alveolar hypoventilation leads to hypercapnia and alveolar hyperventilation results in hypocapnia.[14,26]

Renal Excretion of Fixed Acids

The kidneys are involved in the disposal of the fixed acids produced daily. Since acid production and excretion are identical in a steady state, measurement of urinary acid excretion permits quantification of net acid production.[27] This precise linkage between the tissue production of acids and the renal excretion of acids occurs as follows. The release of fixed acids from the cells generates H^+ and anions. The H^+ decomposes extracellular HCO_3^-, which is excreted as CO_2, and the anion binds the Na^+ previously bound to the decomposed bicarbonate. The amount of decomposed bicarbonate is identical to the amount of added fixed acids of both organic and inorganic origin. The sodium salts of the fixed acids released by the tissues reach the kidney for excretion. To maintain acid-base balance, the kidney must fully reclaim the filtered HCO_3^- as a first step in accomplishing its task of excreting the daily acid load. Daily renal HCO_3^- reabsorption is approximately 4,320 mEq/d (180 L/d of glomerular filtration rate × 24 mEq/L of [HCO_3^-]). Thus, the magnitude of H^+ secretion required to reclaim all the filtered HCO_3^- is approximately 50 times greater than that required for net daily acid excretion. Reclamation of filtered bicarbonate involves secretion of hydrogen ions into the luminal fluid, leading to the net removal of luminal bicarbonate and its incorporation to the intravascular compartment. The proximal tubule is the site of most bicarbonate reclamation (reabsorption) of the filtered bicarbonate.[28] This process is largely (about 2/3 of total) mediated by an Na^+–H^+ antiporter that exchanges one sodium for one proton. A vacuolar H^+ pump is responsible for the remaining one third of the proximal tubular bicarbonate reabsorption. The Na^+–H^+ antiporter represents a secondary active transport that has the low intracellular [Na^+] as the driving force for H^+ secretion. The low intracellular [Na^+] is in turn produced by the basolateral Na^+–K^+ pump (primary active transport).

Table 3. Normal Acid-Base Composition

	Mean	Range
Arterial Blood		
pH	7.40	7.36–7.44
[H$^+$] (nM)	40	36–44
P_{CO_2} (mm Hg)	40	36–44
[HCO_3^-] actual (mM)	24	22–26
[HCO_3^-] standard (mM)	24	22–26
Base excess (mM)	0	−2, +2
Venous Blood		
pH	7.38	7.34–7.42
[H$^+$] (nM)	42	38–46
P_{CO_2} (mm Hg)	46	42–50
CO_2 total (mM)	26	23–30

P_{CO_2} = partial pressure of carbon dioxide

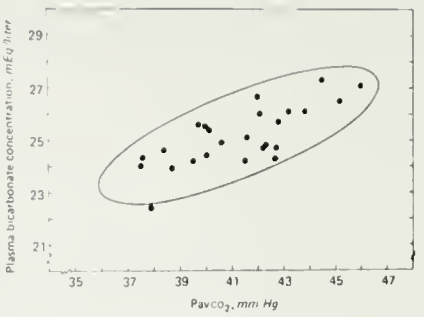

Fig. 3. Dependence of bicarbonate concentration on partial pressure of carbon dioxide in arterialized venous blood (P_{avCO_2}) in the normal state. The 90% confidence region, depicted as a solid line, is for a simple blood sample. (From Reference 29, with permission.)

Complete reabsorption of the filtered HCO_3^-, although of critical importance for the maintenance of acid-base balance, is not responsible for renal excretion of the metabolically produced acids.[1,2] To accomplish the "net acid excretion" the kidney must regenerate the HCO_3^- decomposed in the tissues by exchanging the cation (usually Na^+) bound to the filtered anion (organic or inorganic, derived from the endogenous acid production) for H^+ secreted by the renal tubules, thus producing the urinary titratable acidity. The hydrogen ions secreted for bicarbonate regeneration are buffered in the tubular lumen by titratable buffers and by ammonia (NH_3). Excretion of acid by the kidney with simultaneous maintenance of Na^+ and K^+ balance is also accomplished by the production within the kidney of the organic cation NH_4^+, which can be excreted with the filtered anion. Secretion of H^+ in the distal nephron occurs mostly in the alpha intercalated cell of the collecting duct. These cells secrete protons to the luminal fluid by an H^+ ATPase and an H^+/K^+ ATPase. Whereas the H^+ ATPase is an electrogenic pump, the H^+/K^+ ATPase is electroneutral. The regulation of distal acidification is mediated by changes in hydrogen secretion by the intercalated cells of the collecting duct.

To simplify matters we indicated that the H^+ derived from fixed acids generated by cell metabolism decompose exclusively extracellular bicarbonate, but, in fact, these acids titrate all body buffers and the explanation provided also applies for the case of non-HCO_3^- buffers. In summary, the role of the kidney in acid-base balance resides in the modulation of $[HCO_3^-]_p$. This is done by adjusting the net acid excretion (sum of titratable acidity and urinary NH_4^+) to a level that will maintain normal acid-base balance. Under most conditions, net acid excretion is precisely adjusted in accordance to "endogenous acid production," dietary intake of acid/alkali, and bicarbonate loss in normal stools of 20–40 mmol/d.

Normal Acid-Base Composition

The [H^+] of extracellular fluid is maintained at relatively low levels or, in other words, in the alkaline range by homeostatic mechanisms that result in a 20:1 ratio of [HCO_3^-] to H_2CO_3, when the values are expressed in mmol/L. Table 3 shows the normal blood acid-base composition in adults. These values are notably stable in each subject. Thus, daily variations in resting values for arterial partial pressure of carbon dioxide (P_{aCO_2}) and $[HCO_3^-]_p$ rarely exceed 2–3 mm Hg and 1–2 mEq/L, respectively. On the other hand, normal values for plasma bicarbonate in humans range from 22 to 27 mEq/L, but the factors accounting for this considerable variability had never been systematically examined. However, studies summarized in Figure 3 and Table 4 have addressed this issue. As shown, values for plasma bicarbonate concentration *within the normal range* are highly dependent on the prevailing level of P_{aCO_2}.[29] This relationship appears to account for a substantial fraction of the variability in the level of plasma bicarbonate encountered among normal humans. Indeed, the

Table 4. Normal Plasma Acid-Base Values in Arterialized Venous Blood at Different Carbon Dioxide Tension Levels*

P_{avCO_2} (mm Hg)	$[HCO_3^-]_p$ (mM)	pH
38	23.5–24.7	7.40–7.42
39	23.4–25.4	7.38–7.42
40	23.6–25.9	7.38–7.42
41	23.9–26.4	7.37–7.41
42	24.3–26.7	7.37–7.41
43	24.8–26.9	7.37–7.40
44	25.4–27.0	7.37–7.39

*The range of bicarbonate concentration ($[HCO_3^-]_p$) and pH represent the 90% joint confidence region of the mean steady state values

$[HCO_3^-]_p$ = concentration of bicarbonate in plasma

P_{avCO_2} = carbon dioxide tension in arterialized venous blood

(Adapted from Reference 29.)

correlation coefficient of the relationship between plasma bicarbonate and P_{CO_2} ($r = 0.73$) in arterialized venous blood observed in those studies indicates that some 50% ($r^2 = 0.53$) of the variability in normal plasma bicarbonate concentration in humans is attributable simply to the distribution of normal P_{aCO_2} values.

The sources of the residual variability remain uncertain. However, among normal subjects dietary differences probably play some role (see below). The data indicate that in normal humans a variation of 1 mm Hg in P_{CO_2} from arterialized venous blood is associated with a 0.36 mEq/L change in the same direction in $[HCO_3^-]_p$. Limits of the 90% joint confidence region for plasma acid-base values at different levels of arterialized venous P_{CO_2} show that in normal individuals with P_{CO_2} of 45 mm Hg, the expected $[HCO_3^-]_p$ and blood pH are 25–28 mEq/L and 7.35–7.40, respectively, whereas in subjects with P_{CO_2} of 38 mm Hg, the expected $[HCO_3^-]_p$ and blood pH are in the range of 23–25 mEq/L and 7.38–7.43, respectively.[29] The difference in acid-base composition between arterial and venous blood from a resting extremity is small; venous blood pH is 0.01 to 0.03 lower, P_{CO_2} is about 6 mm Hg higher, and $[HCO_3^-]$ is about 2 mEq/L higher than that of arterial blood. The higher P_{CO_2} in venous blood reflects the interposition of peripheral tissues, which add CO_2 to venous blood. Venous blood can be "arterialized" in vivo by warming up the hand at 45° C for 10 minutes—a procedure that renders the arteriovenous acid-base differences negligible.

Several physiologic factors modify the acid-base status.[1] Compared with the recumbent position, sitting and standing lowers P_{CO_2} by about 3 and 4 mm Hg, respectively. Normal women, during the progesterone phase of the menstrual cycle, have P_{aCO_2} values about 2–4 mm Hg lower, $[HCO_3^-]_p$ about 1 mEq/L lower, and pH about 0.01 to 0.02 higher than in men. Women develop substantial hypocapnia during pregnancy, most notably in the last trimester, with P_{aCO_2} of 29–32 mm Hg, increased alveolar ventilation being driven by the high progesterone levels.

Acid-base composition is influenced by age. Whereas normal children have P_{aCO_2} values of 33–37 mm Hg up to age 3, the difference is progressively minimized such that P_{aCO_2} shifts to 35–40 mm Hg by age 15 years and becomes identical to adult values by age 17 years.

Diet influences the acid-base status through changes in endogenous acid production. Consequently, a small but detectable decrease in both $[HCO_3^-]_p$ and P_{aCO_2} is observed with a meat diet, as opposed to a vegetable diet; nonetheless, despite this difference, the acid-base values are generally maintained within the normal range. High-altitude residents or individuals ascending to high altitudes express hypoxemia-induced hyperventilation, such that the acid-base values reflect primary hypocapnia (respiratory alkalosis).

Limitations of Arterial Blood Sampling

The most commonly used means to assess a patient's acid-base status are arterial blood pH, P_{aCO_2}, and plasma bicarbonate concentration. Measurement of arterial blood pH and P_{aCO_2} and calculation of plasma bicarbonate are performed in the blood-gas laboratory, whereas measurement of plasma total CO_2 from a venous blood sample is performed in the chemistry laboratory (plasma bicarbonate makes up about 95% of total CO_2, such that plasma total CO_2 and bicarbonate concentrations are used interchangeably).

The information obtained using arterial blood gas samples may not always reflect systemic acid-base composition.[30,31] In states of severe circulatory failure, arterial hypocapnia may coexist with venous and, therefore, with tissue hypercapnia. However, the body CO_2 stores have been enriched, and respiratory acidosis rather than respiratory alkalosis is present (Figs. 4 and 5). This entity, which has been termed pseudorespiratory alkalosis, develops in patients with profound depression of cardiac function and pulmonary perfusion but relative preservation of alveolar ventilation, including patients with advanced circulatory failure and those undergoing cardiopulmonary resuscitation. The severely reduced pulmonary blood flow limits the CO_2 delivered to the lungs for excretion, thereby increasing the venous P_{CO_2}. On the other hand, the increased ventilation-to-perfusion ratio causes a larger than normal decrease of CO_2 per unit of blood traversing the pulmonary circulation, thereby giving rise to arterial eucapnia or frank hypocapnia. A progressive widening of the arteriovenous difference in pH and P_{CO_2} develops in these two settings of cardiac dysfunction, namely circulatory failure and cardiac arrest (see Fig. 5). Severe oxygen deprivation prevails in the tissues in these two conditions, and it can be completely disguised by the reasonably preserved arterial oxygen values. Appropriate monitoring of acid-base composition and oxygenation in patients with advanced cardiac dysfunction requires mixed or central venous blood sampling (from either a central venous catheter or a Swan-Ganz catheter, if available) in addition to the sampling of arterial blood.

Alkali Loading

Because bicarbonate-rich solutions are frequently prescribed, especially in intensive care units, it is mandatory to properly understand their effects on acid-base status.[33,34] To determine the expected response to an alkali infusion in terms of the increase in $[HCO_3^-]_p$, it is necessary to express its value in milliequivalents per kilogram of body weight. This practice allows correction for differences in the size of the fluid compartments among patients. A second reason for expressing the alkali load in milliequivalents per kilogram of body weight is the units in which the

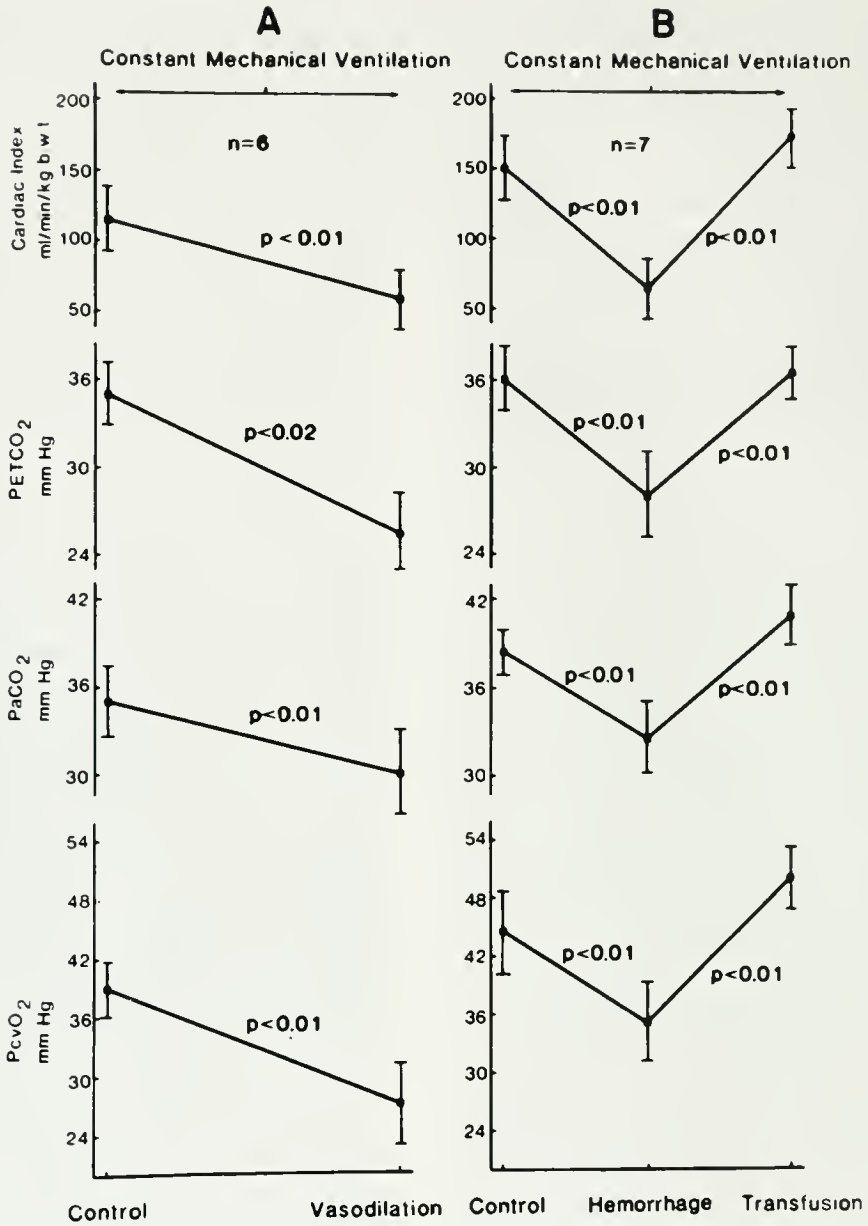

Fig. 4. Reduction in end-tidal partial pressure of carbon dioxide (P_{ETCO_2}), arterial partial pressure of carbon dioxide (P_{aCO_2}), and central venous partial pressure of oxygen (P_{cvO_2}) as a result of diminished cardiac index because of (A) pharmacologic vasodilation or (B) hemorrhage (changes reversed by transfusion) in the presence of constant pulmonary ventilation. (From Reference 30, with permission.)

change in $[HCO_3^-]_p$ is reported (mEq/L). Remember that 1 kg of body fluid amounts to about 1 L of fluid, such that the two units cancel out when one is divided by the other.

The space of distribution of bicarbonate can be viewed as having two components: an anatomic portion and a nonanatomic one. The anatomic portion corresponds to the extracellular fluid volume in which the infused HCO_3 is freely dissolved. The nonanatomic portion is a theoretical space large enough to accommodate, at the prevailing $[HCO_3^-]_p$, all of the administered HCO_3^- unaccounted for by the anatomic boundaries. A large fraction of the nonanatomic portion corresponds to the component decomposed by the body buffers.

The major influences on the size of each component of the "bicarbonate space" are as follows. The anatomic portion is increased in patients with substantial edema, featuring a major expansion of extracellular fluid volume. The opposite is true for patients experiencing severe volume

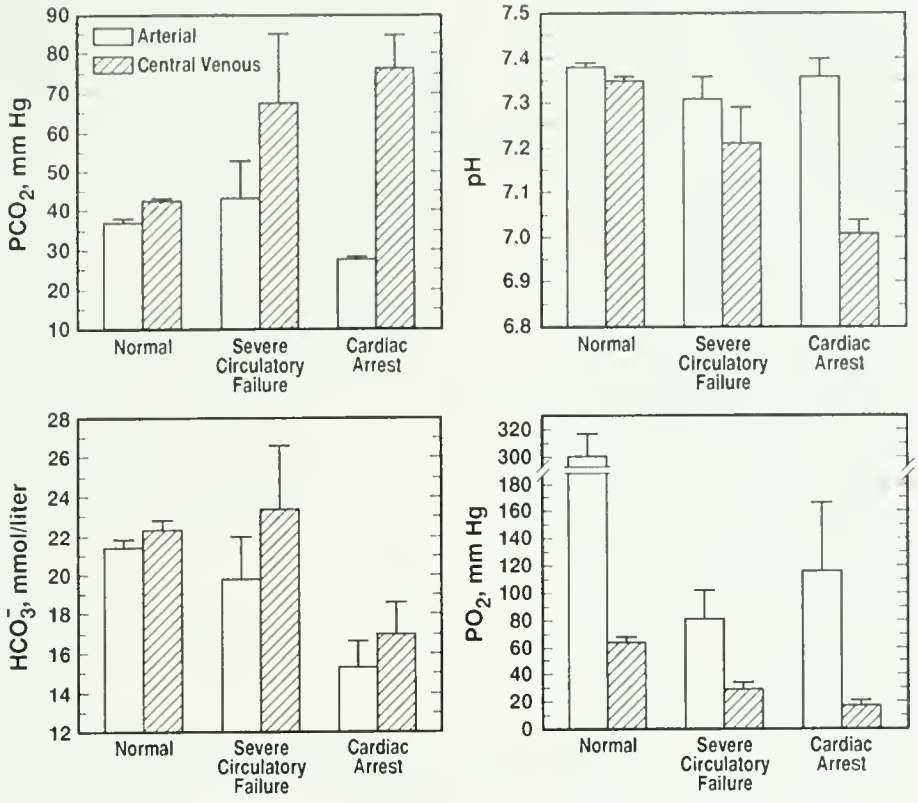

Fig. 5. Simultaneous means (plus standard error) of arterial and central venous values for partial pressure of carbon dioxide (P_{CO_2}), pH, bicarbonate concentration ($[HCO_3^-]$), and partial pressure of oxygen (P_{O_2}) in patients with normal hemodynamic status, patients with severe circulatory failure, and patients with cardiac arrest undergoing cardiopulmonary resuscitation. (From Reference 32, with permission.)

depletion (contraction of extracellular fluid volume). The nonanatomic portion is largely modified by two factors:

1. The initial level of $[HCO_3^-]_p$, because low $[HCO_3^-]_p$ expands the HCO_3^- space and high $[HCO_3^-]_p$ contracts it, and

2. The time elapsed from HCO_3^- loading to that of the evaluation of the plasma bicarbonate response.

This effect is caused by slow equilibration of tissue buffers as well as by the effects of endogenous acid production. The impact of the initial $[HCO_3^-]_p$ and time elapsed on the bicarbonate space has been examined experimentally in dogs (Fig. 6).[33] The empirical equation obtained from those studies, which determines the magnitude of the bicarbonate space as a function of the prevailing plasma bicarbonate is, at the 30-minute mark from the infusion, as follows:

$$\text{bicarbonate space} = 0.36 + \frac{2.44}{[HCO_3^-]_p} \quad (9)$$

The bicarbonate space of normal subjects, measured at 30 minutes following alkali administration, is approximately 50% of body weight. Patients with moderate metabolic acidosis having an $[HCO_3^-]_p$ of 12–20 mEq/L feature a bicarbonate space of about 60–80% of body weight, whereas those with extreme metabolic acidosis (ie, $[HCO_3^-]_p \leq 5$ mEq/L) can exhibit a bicarbonate space that exceeds 100% of body weight. A reduction in the bicarbonate space is observed in metabolic alkalosis, average values being in the range of 30–40% of body weight. As shown in Figure 6, there is a substantial time-dependent increase of the bicarbonate space, which averages about 10% of body weight at 60 minutes.

Let us now determine the expected increase in $[HCO_3^-]_p$ in response to administering 4 mEq/kg body weight of $NaHCO_3$ to a normal individual whose weight is 50 kg (ie, 200 mmol of alkali). In the normal state, the apparent space of distribution of the alkali (bicarbonate space) is, as explained above, approximately 50% of body weight; thus, the expected increase in $[HCO_3^-]_p$ in our subject is as follows:

$$\Delta[HCO_3^-]_p = \frac{4 \text{ mEq/kg (alkali load)}}{0.5 \text{ (ie, 50\%, bicarbonate space)}}$$

$$= 8 \text{ mEq/L} \quad (10)$$

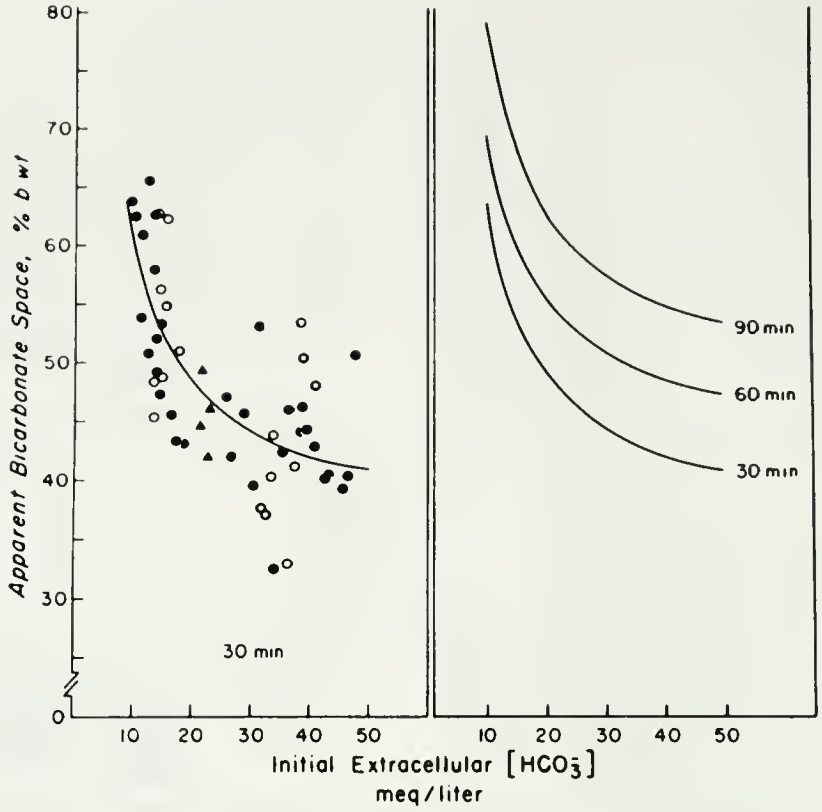

Fig. 6. Relationship between initial extracellular bicarbonate concentration ($[HCO_3^-]$) and apparent bicarbonate space following sodium bicarbonate infusion. The left-hand panel depicts the relationship at 30 minutes after infusion. Filled circles denote values obtained in dogs with metabolic acid-base disturbances. Open circles denote values in dogs with respiratory acid-base disturbances. Filled triangles denote values in dogs with normal acid-base status. (From Reference 33, with permission.)

This calculation demonstrates that the expected increase in $[HCO_3^-]_p$ after an alkali load in the presence of a normal bicarbonate space amounts to the alkali load expressed in milliequivalents per kilogram of body weight multiplied by 2. As indicated by the above equation, dividing the administered HCO_3^- load by the observed change in $[HCO_3^-]_p$ permits an empiric estimation of the bicarbonate space. For example, if administration of an alkali load of 4 mEq/kg of body weight had resulted in a change in $[HCO_3^-]_p$ of 5 mEq/L, the bicarbonate space, expressed as a percentage of body weight, would be as follows:

$$\text{bicarbonate space} = \frac{4 \text{ mEq/kg (alkali load)}}{5 \text{ mEq/L } (\Delta[HCO_3^-]_p)} \times 100$$

$$= 80\% \quad (11)$$

Administering 1 mEq of sodium bicarbonate (ie, 1 mL of the usual 1-N preparation) per kilogram of the patient's body weight will increase plasma bicarbonate by 1 or 2 mEq/L for a bicarbonate space of 100% or 50% of body weight, respectively. Being mindful of the possibility of overtreatment, we recommend that bicarbonate requirements be calculated on the basis of a bicarbonate space of 50% of body weight. Thus, to raise plasma bicarbonate from an initial value of 4 mEq/L to a target value of 8 mEq/L, one should administer 2 mEq of sodium bicarbonate per kilogram of the patient's body weight. Except in the case of extreme acidemia, sodium bicarbonate should be dispensed as an infusion (over several minutes to a few hours) rather than as a bolus. Subsequent monitoring of the patient's acid-base status will determine whether additional alkali will need to be administered. In this regard, about 30 minutes must elapse following completion of the infusion before the clinical effect of a bicarbonate load is judged.

Acid Loading

Acid infusions are occasionally used in the management of patients with metabolic alkalosis, especially when the pace of correction of the disorder must be accelerated.[32] The distribution of an acute acid load within body fluids is

virtually complete within 20 to 30 minutes. Buffering of the hydrogen ions takes place promptly in the extracellular fluid and within cells, and the relative buffering contribution of each of these compartments occurs at a 1:2 ratio. Computation of the amount of acid to be infused is based on a volume of distribution of the acid load equal to a bicarbonate space of 50% of body weight. The solution most commonly used is 0.1 N hydrochloric acid (HCl), thus containing 100 mEq of H^+/L. To reduce plasma bicarbonate concentration, for example, from 50 mEq/L to 40 mEq/L in a 70 kg patient, the amount of H^+ required can be estimated as $10 \times 70 \times 0.5$, or 350 mEq. This amount of H^+ is contained in 3.5 L of HCl solution. Some clinicians might find it more expedient to base the prescription on the fact that infusion of 5 mL of HCl solution per kilogram of the patient's body weight will decrease plasma bicarbonate concentration by about 1 mEq/L—a proportionality that incorporates the values for the bicarbonate space and the normality of the solution. Although highly effective, infusion of HCl, as well as other acidifying agents (eg, NH_4Cl, arginine monohydrochloride), entails considerable risks.

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Metabolic Acidosis

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Introduction
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  Chemical Buffering
  Respiratory Compensation
  Changes in Intermediary Metabolism
  Renal Compensation
Consequences of Metabolic Acidosis
Recognition and Diagnostic Strategy
Etiologies of Metabolic Acidosis
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Treatment of Metabolic Acidosis
Summary

Metabolic acidosis occurs in a number of diseases and even certain normal activities such as heavy exercise. It arises from increased endogenous acid production, exogenous acid (or acid-precursor) administration, base losses, and depression of renal acid secretion. Although the magnitude of acidosis is important, the ultimate pathophysiological impact of any metabolic acidosis is defined by the rate of change and the specific cause of the acidosis. This review discusses whole body, organ, and cellular effects of metabolic acidosis, its diagnosis by pathophysiologic categories, and treatment. The diagnosis is made by a synthesis of the clinical history, physical examination, other hematological values, serum and urinary chemistries, and arterial blood gases and electrolytes. Calculation of the anion and osmolal gaps can be effectively used to further narrow the diagnostic possibilities. Supportive care and therapy directed at the cause of the metabolic acidosis are the mainstays of treatment, since most acidotic states will spontaneously correct once the initiating cause is removed or reversed. Theoretical and clinical evidence are discussed for alkalinizing agents, whose use remains controversial except in the treatment of metabolic acidosis associated with hyperkalemia and certain drug or toxin ingestions. *Key words: metabolic acidosis, acid-base, acidosis, alkalosis, bicarbonate therapy, respiratory compensation, intracellular pH.* [Respir Care 2001; 46(4):342–353]

Introduction

Metabolic acidosis is a common problem accompanying and complicating a large number of diseases, especially those in critically ill patients, whose care routinely involves respiratory therapists. Thus, a basic understanding of acid-base pathophysiology at the cellular, organ, and whole body level is key to understanding the diagnostic and therapeutic approaches to metabolic acidosis. This review focuses largely on the common varieties of metabolic acidosis encountered in hospital practice, emphasizing the need to appreciate the multiple causes of metabolic acidosis, gauge their severity, and provide cause-related therapy and base repletion when appropriate.

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Pathophysiology

Metabolic acidosis can be defined as a pathophysiologic process characterized by primary decrease in plasma bi-

carbonate concentration to less than 22 mEq/L. Other nonbicarbonate alkaline buffers are also reduced, but because of the unique properties of the CO_2-HCO_3^- buffer pair, roughly 80–90% of total metabolic acid buffering is accomplished by bicarbonate consumption. With the exception of renal compensation for respiratory alkalosis, which does not lower HCO_3^- below 10 mEq/L, all hypobicarbonatemia is abnormal. In the absence of preexisting respiratory or metabolic alkalosis, or a concurrent counteracting alkalinizing processes, a decrease in bicarbonate will result in acidemia (an acidification of plasma and extracellular space: pH < 7.35).

Response to an Acid Load

Consider the reaction of H^+ with the primary extracellular buffer, HCO_3^-, or other buffers (Buf):

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

$$H^+ + Buf^- \leftrightarrow HBuf \quad (1)$$

We can see that metabolic acidosis can be produced in two ways: by addition of H^+ ions or by loss of HCO_3^- or other buffers. Compensation for an increase in H^+ involves several processes, each with different time courses, effectiveness, and utilization: extracellular buffering, passive intracellular and bone buffering, active intracellular pH defense and organic acid uptake and metabolism, respiratory compensation, increased renal excretion of acid, and increased retention of nonbicarbonate bases generated in the digestion of foods by the gastrointestinal tract. These compensatory processes are discussed more fully elsewhere in this issue of RESPIRATORY CARE[1] and are therefore only briefly reviewed herein. The effectiveness of each of these processes may be considerably diminished in many patients with severe metabolic acidosis, depending on the severity of the acidosis, and if there is underlying cardiac, pulmonary, renal, or hepatic insufficiency.

Chemical Buffering

Both in and outside of cells, titration of buffers occurs within minutes and is the most immediate compensation. It is largely accomplished by consumption of HCO_3^- and generation of CO_2, which is exhaled via the lungs. The excess CO_2 produced by this buffering is readily excreted, with little demand on the respiratory system, since it represents a trivial percent (< 1%) of normal metabolic CO_2 production. In the extracellular space, HCO_3^- is the only substantial buffer, whereas in cells the buffers include HCO_3^- (at roughly one half the extracellular concentration), proteins, phosphates, amino acids, and bone carbonate. About 55–60% of an acid load will be buffered by cells and bone buffers.

In addition to passive chemical buffering, it is clear that cells of many critical organs have an extraordinary capacity to defend their own intracellular pH. In view of the marked pH sensitivity in virtually all cellular processes,[2] the importance of intracellular pH regulation is hardly surprising. With the exception of red cells, all cells appear to have intracellular pH values that are appreciably more alkaline than would be predicted if H^+ and HCO_3^- were passively distributed across the plasma membrane. Transmembrane pH differences vary among tissues but range between 0.2 and 0.5 units,[3] in contrast to the 0.8 to 1.5 unit difference that would occur in the face of no intracellular pH regulation. The same transmembrane ion exchanges that help to maintain intracellular pH above that dictated by passive electrochemical forces can also be stimulated selectively in the face of endogenous or exogenous acidoses.[4] These include exchange of extracellular Na^+ for intracellular H^+ via the Na^+–H^+ membrane antiporter, and active H^+ extrusion by proton translocating adenosine triphosphate-ases (ATPases). Critical tissues and organs such as the heart,[5] brain,[6] liver,[7] respiratory muscles,[8] and kidneys[9] have remarkable capacity to defend their pH. The rate and magnitude of these responses probably help to explain the surprising tolerance to acidosis and alkalosis in otherwise healthy people without underlying circulatory insufficiency or hypoxemia.[10] Because these mechanisms are linked to ATP hydrolysis, the requirement for adequate oxygen and substrate delivery is obvious. The extent to which key organs can defend their intracellular pH is not easily determined in patients, but animal studies show that when these exchangers are fully activated and operative in acidotic states, brain and heart pH can become more alkaline than the extracellular fluid (ECF).[6] The active defense of intracellular pH may also explain in part why much more HCO_3^- than other intracellular fluid buffers is preferentially consumed in buffering metabolic acidosis, since as H^+ is pumped out of cells it can only be buffered by plasma HCO_3^-.

Intracellular entry of H^+ ions in metabolic acidosis is associated with movement of K^+ into the ECF, in part to maintain electroneutrality, since K^+ is the major cation in cells. This response is variable and dependent on the type of acidosis, being more prominent in nonorganic acidoses and much less so in organic acidoses and respiratory acidosis. Many of the illnesses that generate metabolic acidosis also directly alter K^+ metabolism independent of the acidemia to generate hyperkalemia. The link between H^+ and K^+ movements in metabolic acidosis is clinically more relevant with regard to the ability of administered HCO_3^- to promote intracellular uptake of K^+.

Respiratory Compensation

Metabolic acidosis stimulates both the central and peripheral chemoreceptors controlling ventilation, and if there is no depression of respiratory drive or significant mechanical limitation to breathing, alveolar hyperventilation occurs. The ensuing decrease in partial pressure of carbon dioxide (P_{CO_2}) will raise intracellular and extracellular pH toward but not completely to normal. The more severe the acidosis the less successful is the return of pH toward normal. The rise in ventilation occurs within minutes but may take several hours to reach its fullest expression. The increase is more the result of increased tidal volume than respiratory rate, and may reach a maximum of 25–30 L/min. This degree of hyperventilation, often called Kussmaul's respiration, may cause dyspnea and be appreciated on physical examination.

The expected degree of respiratory compensation has been studied in otherwise normal patients with metabolic acidosis and as a general rule the P_{CO_2} can be expected to decrease 1.2 mm Hg for every 1.0 mEq/L reduction in plasma HCO_3^-, reaching a minimum of 10–15 mm Hg.[11] Deviations from this predicted relationship represent either mixed acid-base disorders, pulmonary limitations, or a rapidly evolving and worsening acidosis such that a steady-state level of ventilation has not been attained. Interestingly, respiratory compensation is only effective in elevating the pH in the acute period, because after several days, the kidneys respond to the lower P_{CO_2} by reducing HCO_3^- reabsorption and permitting some bicarbonate loss. The net effect is that the arterial pH in chronic metabolic acidosis will be the same as in the acute phase whether or not respiratory compensation took place.[12]

Changes in Intermediary Metabolism

Several alterations in intermediary metabolism occur in metabolic acidosis that help to mitigate the extent of acidosis. First, certain enzymes in the glycolytic pathway (such as phosphofructokinase, the activity of which is pH sensitive) are mildly inhibited. This leads to a slight drop in pyruvate and, thus, lactate production. The other important effect of acidosis is to enhance the uptake of lactic and ketoacids by the liver and well perfused skeletal muscle,[13] therefore enhancing the clearance of these acids, particularly when their production elsewhere is increased.

Renal Compensation

The response of the kidneys in regulating systemic acid-base balance is of much slower onset, so that there is very little compensation by the kidney until many hours after the onset of a pH disturbance. The full expression of renal adaptation may take several days and depends on a normal extracellular volume status and renal function. When a metabolic acidosis is not of a renal origin and the rate of acid production or HCO_3^- loss does not exceed 200–250 mEq/d, increased renal H^+ secretion can be fully compensatory.

The normal generation of 50–100 mEq/d of acid in the normal adult diet is excreted by the combination of total reclamation of filtered HCO_3^- (largely in the proximal tubule) and H^+ secretion in the distal tubule. H^+ secretion is accomplished by active H^+-ATPase and H^+/K^+-ATPase pumps. The H^+ ions combine with filtered and secreted titratable buffers in the urine, such as phosphate and sulfate, or with NH_3 generated by deamination of glutamine. In metabolic acidosis of nonrenal origin, the kidney can increase total H^+ excretion by 3–4-fold,[14] principally by increasing NH_3 production and up-regulating the number and activity of H^+-ATPase and H^+/K^+-ATPase pumps.

Consequences of Metabolic Acidosis

Table 1 lists major adverse and few positive consequences of severe metabolic acidemia. The conventional definition of severe acidemia is usually given as an arterial pH less than 7.10, but tolerance to even lower pH is possible in healthy individuals. For example, arterial pH as low as 6.8 has been measured in athletes at maximum aerobic output. What defines the clinical severity more critically must include (1) the cause of the acidosis, (2) its rate of evolution, (3) the ongoing rate of acid production, and (4) the patient's physiologic reserves.

The cardiovascular effects of acidosis are the most serious. Acidosis directly suppresses myocardial contractility and vascular smooth muscle tone, leading to decreased cardiac output and hypotension, with reductions in blood flow to the renal and splanchnic beds. In part, these direct effects are countered by a neurohumoral response consisting of increased sympathetic discharge and cortisol secretion, but this response may be blunted by the adrenergic receptor desensitization that occurs with severe acidosis. Given the complexity of these opposing effects, it is not possible to define a particular pH at which one must intervene to raise the extracellular pH by alkalinizing agents. Certain other effects of metabolic acidosis will be taken up individually as they pertain to the different metabolic acidoses seen in the critically ill.

Recognition and Diagnostic Strategy

As with all acid-base disorders, analysis of arterial blood gas samples and serum electrolytes provide the quantitative basis for diagnosis and treatment. Nonetheless, it is important to stress the utility of the history and physical examination, since they can provide significant clues as to

Table 1 Effects of Metabolic Acidosis

Cardiovascular
Myocardial depression
Desensitization of beta adrenergic receptors
Antagonism of Ca^{2+} influx and action
Systemic arterial vascular smooth muscle relaxation
Antagonism of Ca^{2+} influx and action
Desensitization of alpha adrenergic receptors
Systemic venoconstriction and centralization of blood volume
Pulmonary vasoconstriction
Enhanced hypoxic pulmonary vasoconstriction
Sensitization to re-entry arrhythmias and lower threshold for fibrillation
Neuro-endocrine
Sympathetic nervous system stimulation
Increased cortisol and epinephrine secretion
Cerebral
Ventilatory stimulation
Inhibition of metabolism and cell volume regulation
Increased cerebral blood flow
Respiratory
Hyperventilation
Dyspnea and exercise intolerance
Reduced hemoglobin-oxygen affinity (Bohr effect)
Improved ventilation-perfusion matching
Metabolic
Decreased glycolysis
Increased hepatic and skeletal muscle organic acid uptake
Decreased insulin sensitivity
Increased protein degradation
Renal and Electrolyte
Increased HCO_3^- reabsorption and H^+/NH_4^+ excretion
Hyperkalemia
Others
Osteoporosis and early epiphyseal closure
Blunting of cytokine/oxygen radical/nitric oxide formation

the possible cause, severity, and duration of the metabolic acidosis. The diagnosis first depends on ascertaining that a disorder with a low plasma bicarbonate is associated with an acidemia. If not, then one is dealing with a renal compensation to a primary respiratory alkalosis. The arterial blood gas sample, in addition to confirming the low bicarbonate and acidemia, provides two other critical data. The P_{CO_2} can be used to judge whether the appropriate respiratory compensation is present. If it is higher than expected, one should be concerned about the patient's pulmonary status and whether there is the threat of possible respiratory failure. If it is lower, then a cause for primary respiratory alkalosis should be considered. Finally, the P_{O_2}, hemoglobin, and oxygen saturation are critical in establishing the sufficiency of arterial O_2 content and tissue O_2 delivery.

Once a metabolic acidosis is established, calculation of the plasma anion gap can be used as a first step in differentiating the cause. The sum charge of all anions in plasma must equal the cations, but only certain anions and cations are routinely and rapidly measured.

$$[Na^+] + [\text{unmeasured cations}] = [HCO_3^-] + [Cl^-] + [\text{unmeasured anions}] \quad (2)$$

Unmeasured anions include negatively charged proteins (predominantly albumin, with a charge equivalency of 2 mEq/L for each g/dL), phosphate (2 mEq/L), sulfate (1 mEq/L), lactate (1–2 mEq/L), and ketoacids and other organic acids (3–4 mEq/L). Unmeasured cations include calcium (5 mEq/L), magnesium (2 mEq/L), and gamma globulins. Although K^+ is readily measured, by convention it is given a value of 4 mEq/L and not included in the calculation of the anion gap:

$$AG = [\text{unmeasured anions}] - [\text{unmeasured cations}] = [Na^+] - ([Cl^-] + [HCO_3^-]) \quad (3)$$

wherein AG is the anion gap. The normal value for the anion gap is 10 ± 4 mEq/L if the serum albumin is normal. Deviations upward or downward from normal require a correction of 2.5 mEq/L per g/dL change in albumin concentration. One should be familiar with the reference values of the hospital laboratory, since the methodology (ion selective electrodes that measure free concentrations of ions, or other methods that measure total [free plus bound] concentration) can lead to differences of 2–3 mEq/L in the normal value between laboratories.

Another useful value is osmol gap, which is the difference between the measured osmolality of the plasma and that calculated by the formula:

$$Osm = 2[Na^+] + [\text{glucose}]/18 + [BUN]/2.8 + [\text{ethanol}]/4.6 \quad (4)$$

wherein Osm is osmolality and BUN is blood urea nitrogen. If the measured osmolality is more than 10 above the calculated, then there may be osmotically active particles present, indicative of possible toxins, whose metabolites may be organic acids.

However, marked degrees of ketoacidosis and lactic acidosis can also contribute to an elevation in the osmol gap. Figure 1 provides a diagnostic approach to metabolic acidosis, using the anion gap and osmol gap as critical juncture points.

Etiologies of Metabolic Acidosis

In the clinical setting there are 3 general mechanisms that lead to metabolic acidosis. They include failure of

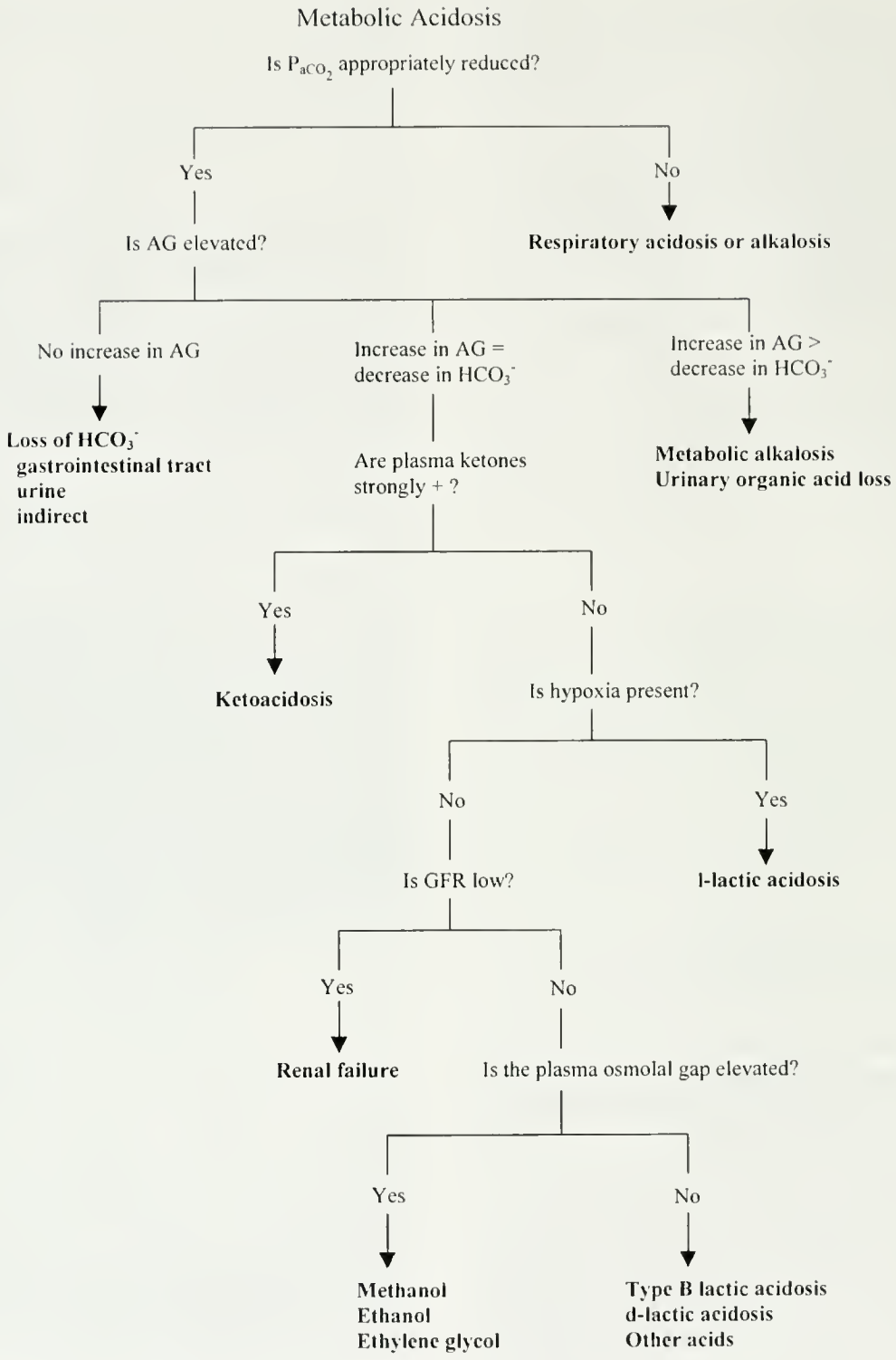

Fig. 1. Diagnostic approach to metabolic acidosis. P_{aCO_2} = arterial partial pressure of carbon dioxide. AG = anion gap. GFR = glomerular filtration rate.

normal renal acid secretion, addition or overproduction of acid, and loss of bicarbonate or alkaline equivalents. Given the large number of conditions causing metabolic acidosis by one or more of these mechanisms, it is beyond the scope of this review to discuss individual conditions in detail. Rather, the focus will be on general principles of

recognition, diagnosis, and treatment. More in-depth attention will be directed to diseases that cause severe metabolic acidosis, in which patients require intensive care, since these patients often are cared for by respiratory therapists. It is in this group, moreover, that much controversy exists surrounding the efficacy and rationale of HCO_3^- therapy. Table 2 lists the clinical causes often encountered and provides a range of rates of acid production of the various categories. In general, hyperchloremic metabolic acidoses result from a loss of bicarbonate, through either the kidneys or the gut, or from the addition of an acid with chloride as the accompanying anion. High anion gap metabolic acidoses result from the ingestion or internal production of organic acids. It should be realized, however, that both forms may coexist in some patients, particularly in those who begin with a hyperchloremic acidosis but develop volume depletion and a subsequent lactic or ketoacidosis. The table, although long, is not an exhaustive list of specific causes. Such comprehensive lists can be found in any major nephrology text.

Table 2. Causes of Metabolic Acidosis

Cause	Rate of Acid Accumulation
Failure of renal acid excretion	2–4 mEq/h
Decreased H^+ secretion	
Distal renal tubular acidosis	
Decreased NH_4^+ production	
Generalized renal failure	
Adrenal insufficiency/hypoaldosteronism	
Loss of bicarbonate and alkaline equivalents	1–20 mEq/h
Gastrointestinal	
Diarrhea	
Pancreatic, biliary and enteric drainage	
Urinary diversion	
Renal	
Carbonic anhydrase inhibitors	
Proximal renal tubular acidosis	
Post-hypocapnic state	
Dilutional Acidosis	
Addition and/or overproduction of acid	2–500 mEq/h
Endogenous	
Lactic acidosis	
Ketoacidosis	
Alcoholic	
Starvation	
Diabetic	
Hereditary metabolic enzyme disorders	
Exogenous	
Acid administration	
Hydrochloric acid	
Ammonium chloride	
Cationic amino acids in total parenteral nutrition	
Toxins converted to acid	
Methanol	
Ethylene glycol	
Paraldehyde	
Salicylate	

Hyperchloremic Metabolic Acidosis

Diarrhea is the most common cause of hyperchloremic metabolic acidosis in the intensive care unit. The intestinal fluids below the stomach, including the pancreatic and biliary secretions, are relatively alkaline, consisting both of HCO_3^- and organic anions, which when absorbed are converted to HCO_3^- in normal metabolism. As a result, diarrhea, vomiting with intestinal obstruction, tube drainage, or fistulas can lead to metabolic acidosis if the rate of base loss exceeds the kidneys' ability to increase NH_4^+ excretion. Occult laxative abuse should always be suspected in a patient with an unexplained hyperchloremic metabolic acidosis. However, laxative abuse can also lead to metabolic alkalosis if the effect is largely in the colon and there is associated K^+ depletion. Urinary diversion, such as ureterosigmoidostomy, may cause a hyperchloremic metabolic acidosis in up to 80% of patients, for two reasons.[15] The first is that the colon has an anion exchanger that exchanges HCO_3^- for the high chloride usually found in urine. Second, the colon can directly absorb NH_4^+, which is derived from urine and colonic bacteria. The absorbed NH_4^+ is converted to NH_3 and H^+ in the liver. Therapy is directed toward volume repletion, antibiotics if appropriate, cessation of laxatives, and other disease-specific therapy.

Renal tubular acidosis either of the type involving the proximal tubule (type 2) or the several forms involving the distal tubule (types 1 and 4) cause mild to moderate hyperchloremic metabolic acidosis.[16] The problem in type 1 renal tubular acidosis and with carbonic anhydrase inhibitors such as acetazolamide is one in which there is inadequate reabsorption of filtered bicarbonate. The decrease in plasma bicarbonate is usually never below 15 mEq/L, because of the remaining HCO_3^- reabsorptive capacity of the proximal tubule and the intact reabsorptive capacity of the distal tubule. The distal renal tubular acidoses are characterized by a defect in distal H^+ secretion, which reduces both titratable acid and NH_4^+ secretion. As with proximal renal tubular acidosis, the severity of the acidosis is generally mild. Generalized renal failure in its early phase may simply present with a hyperchloremic metabolic acidosis, but this shortly develops into a high anion gap acidosis as numerous unmeasured anions normally excreted in the urine are retained. Therapy is oral HCO_3^- replacement or withdrawal of carbonic anhydrase inhibitors.

The phenomenon of dilutional acidosis is sometimes seen in the intensive care unit during very aggressive volume resuscitation (> 50% of normal ECF volume) with bicarbonate-free or base equivalent-free containing solu-

tions such as saline.[17] There is no actual loss of bicarbonate, but the expected dilution of extracellular HCO_3^- is mitigated as intracellular and bone nonbicarbonate base stores are mobilized and transferred to the extracellular space. However, if there is preexisting metabolic acidosis and depletion of base stores, the dilutional acidosis may account for a significant degree of acidemia. Usually the condition is self-limited as the kidneys generate new bicarbonate and the natriuresis and diuresis (of an acidic, bicarbonate-free urine) with resolution of the original need to use resuscitative fluids brings the ECF volume back to normal.

Administration of HCl or metabolic equivalents such as cationic amino acids in hyperalimentation fluids can overwhelm limited renal function in some patients and generate a hyperchloremic metabolic acidosis. The problem can be easily dealt with by supplementation with base equivalents added to the solutions.

A primary respiratory alkalosis leads to compensatory loss of HCO_3^- in the urine. When the process initiating the hypocapnia abates, the P_{CO_2} rises relatively quickly and the original state of alkalemia converts to an acidemia. This may persist for 2–4 days as the kidney takes on the somewhat slower process of new bicarbonate generation, as occurs in the correction of a dilutional acidosis.

High Anion Gap Metabolic Acidosis

The anion gap is very useful in generating a differential diagnosis, but until the value is more than 20 the acidosis is usually not severe, and it is not often easy to identify the responsible organic acid. Anion gaps less than 20 are most often secondary to changes in proteins, phosphates, or other charge equivalents.[18] When the anion gap exceeds 30, the organic acidosis is usually diagnosable. However, minor elevations in the anion gap should not be ignored, despite the greater likelihood that a cause will not be found. Critically ill patients often have hypoalbuminemia, and this will cause the anion gap to be lower than it otherwise would be and mask the severity of the acidosis.

The generation of protons decreases the concentration of bicarbonate. If the acidosis occurs by the gain of protons and chloride, or by loss of bicarbonate, the change in bicarbonate is matched by the change in chloride, leading to no change in the anion gap. However, if it is caused by a gain of an organic acid, the HCO_3^- decreases and there is an increase in an unmeasured anion. Theoretically the increase in the anion gap above normal, the so-called "delta anion gap," should equal the decrease in bicarbonate (delta bicarbonate), and the delta anion gap to delta bicarbonate ratio should be one; however, it should be remembered that H^+ can be buffered by other titratable substances. The extent to which this happens depends on the severity of the acidosis and the particular disease. Another means by which a one-for-one ratio is altered is secondary to the loss of the organic anion in the urine, with replacement by chloride. Lastly, if there is a pre-existing metabolic acidosis or metabolic alkalosis, the apparent one-for-one ratio will not be evident. These factors can cause the ratio to vary between 0.8 and 1.6. Given all the above caveats, it is generally fruitless to seek additional acid-base disturbances unless the ratio falls outside that range.

Lactic acidosis is the most common anion gap acidosis encountered in the intensive care unit. It is often the most severe and difficult-to-treat form of all metabolic acidoses.[19] Table 3 gives a more complete list of the multiple causes of lactic acidosis. The normal lactate concentration is 1–2 mEq/L, which represents the equilibrium between production and consumption in normal metabolism of

Table 3. Causes of Lactic Acidosis

Increased oxygen consumption
Strenuous exercise
Grand mal seizure
Respiratory alkalosis
Hypothermic shivering
Neuroleptic malignant syndrome
Pheochromocytoma
Decreased oxygen delivery
Decreased cardiac output
Hypovolemia
Cardiogenic shock
Myocardial, valvular, pulmonary vascular, pericardial
Decreased arterial oxygen content
Severe anemia and hypoxemia
Regional ischemia
Mesenteric and peripheral
Microcirculatory disorders
Sepsis
Altered cellular metabolism
Diabetes mellitus
Thiamine deficiency
Hypoglycemia
Malignancy
Toxins and drugs
Carbon monoxide
Ethanol/methanol
Cyanide
Salicylates
Nitroprusside
Zidovidine
Cyclosporine
Hereditary metabolic enzyme disorders
Decreased lactate clearance
Hepatic failure
Miscellaneous
d-lactic acidosis with short bowel syndrome or stasis
Acquired immunodeficiency syndrome
Severe rhabdomyolysis

1,000–1,500 mEq/d. It is easy to appreciate that only a slight imbalance between production and consumption (either increased production or decreased clearance) can lead to hyperlactemia. Thus, with just the sympathetic stress and hypermetabolism of most critical illnesses, it may rise to 2–5 mEq/L. Any degree of metabolic or respiratory alkalosis can stimulate glycolysis and increase serum lactate by 2–3 mEq/L.

Lactic acidosis of clinical importance and consistent with possible tissue hypoxia is usually characterized by acidemia and lactate greater than 5 mEq/L. Although in cardiogenic shock lactate levels correlate with mortality, that is not the case in many other forms of lactic acidosis. A large overlap exists in values of survivors and nonsurvivors, owing to such factors as the primary disease, nutritional status, and hepatic lactate clearance. However, in the individual, the trend in lactate concentration can be helpful in gauging therapy and assessing prognosis. In addition to the acidemia of lactic acidosis, there are potentially negative effects of lactate itself, which may add to the clinical problem. Lactate may further aggravate the adrenergic desensitization of acidosis, reduce glycolysis, impair mitochondrial oxygen utilization, and depress inward Ca^{2+} currents that activate myocardial contraction.[20]

Sepsis is a common cause of lactic acidosis and several mechanisms account for the increased lactate acid.[21] These include frank reductions in tissue oxygen delivery and obligatory anaerobic metabolism with hypoperfusion and myocardial depression. Even in the presence of a hyperdynamic circulation there may be occult tissue hypoxia because of maldistribution of blood flow at the microcirculatory level. Sepsis is a hypermetabolic state with increased substrate flux, such that increased glycolysis and protein breakdown lead to excess pyruvate production in excess of mitochondrial needs.

Grand mal seizures cause profound muscle energy use in a short interval.[22] The tremendous glycolysis necessary to sustain seizure activity can lead to lactate elevations of more than 15 mEq/L and pH below 7.10. The acidemia may also be aggravated by CO_2 retention from hypoventilation during the seizure interval. The lactate can be readily reconverted to bicarbonate in the post-seizure period.

Lactic acidosis can occur with some malignancies, most commonly in leukemias and lymphoma.[23] In tumor cells there is enhanced glycolysis with loss of the normal cellular control mechanisms that tightly couple glycolysis with oxidative phosphorylation. If there is extensive hepatic infiltration of metastatic tumor, decreased lactic acid clearance by the liver will further compound the magnitude of lactate accumulation.

D-lactic acidosis is an interesting form of lactic acidosis, since the anion in all other forms is l-lactate.[24] Most lactate assays will only measure the l-isomer of lactic acid, so the diagnosis will not be made on routine lactate measurement. d-lactic acid levels in blood and urine must be specifically ordered. d-lactic acid is a byproduct of certain Gram-positive bacteria. When intestinal conditions permit their unchecked growth in the presence of large amounts of carbohydrate, large amounts of d-lactic acid are absorbed by the colon. This can occur in patients with short bowel syndrome and in those with blind loops or intestinal stasis from other causes. The therapy is enteral calorie restriction, facilitation of gut motility, and sometimes antibiotics.

Ketoacidosis can develop with starvation, insulin deficiency, and heavy alcohol intake. It occurs when there is an increase in free fatty acid production and a preferential shunting of fatty acids to the liver for ketoacid rather than triglyceride formation. This situation is favored when insulin levels are low and glucagon is elevated.

In starvation, insulin levels decrease and glucagon rises, favoring fatty acid mobilization and ketoacid formation. The ketoacidosis is mild,[25] with total ketoacid concentration not exceeding 10 mEq/L. Ketoacid formation stimulates insulin secretion and this is what probably prevents runaway ketoacid production in simple fasting.

In alcoholic ketoacidosis, usually in the setting of binge drinking and poor dietary intake, the normal fasting ketoacidosis is aggravated by the effect of ethanol to enhance lipolysis, further increasing the supply of free fatty acids.[26] However, other factors act to worsen an already unbalanced metabolic state. With vomiting and its attendant volume depletion, catecholamine secretion is increased, which drives lipolysis and depresses insulin sensitivity. These factors, in addition to a concurrent lactic acidosis, can generate a severe degree of acidosis. The therapy is volume repletion with glucose supplementation and avoidance of alcohol.

Diabetic ketoacidosis is the most common cause of ketoacidosis in the intensive care unit. The problem is a primary insulin deficiency (and, secondarily, insulin receptor insensitivity) leading to hyperglycemia, increased free fatty acid production, osmotic diuresis, electrolyte abnormalities, and marked volume depletion.[27] The degree of acidemia can be quite profound, with arterial pH below 7.00. The therapy is volume and electrolyte repletion and provision of insulin.

A wide variety of toxins and drugs can lead to high anion gap acidoses when the metabolism of the toxin yields an organic acid. Thus, any patient presenting with a high anion gap acidosis that cannot be explained by tests showing high lactate or ketoacid concentrations should be suspected of having ingested a toxin. It should be remembered that in some toxin cases there may be associated mild lactic and ketoacidosis. Specific urine and blood toxin screens should be used, but their turnaround time is often not fast and many toxins may not be picked up. A very useful test employed to raise the suspicion of a toxin is

calculation of the osmol gap. If the measured osmolality is more than 10 above the calculated, then there are osmotically active particles present, such as ethanol or ethylene glycol.

Treatment of Metabolic Acidosis

The treatment of any metabolic acidosis involves initiating effective therapy to deal with the underlying or primary cause of the acidosis and then assessing the need to directly reverse the acidemia with some form of alkalinizing therapy. In many cases, the treatment of the underlying cause and attention to normalization of volume, cardiac output, and arterial oxygenation will be sufficient to allow for metabolism of endogenous organic acids (lactate and ketoacids) back to bicarbonate or for the kidney to regenerate new bicarbonate to replace losses. The restoration of normal tissue oxygenation and perfusion is not only necessary to reverse the metabolic pathways leading to organic acid formation; it also allows critical organs to actively defend their intracellular pH by extrusion of H^+ into the extracellular fluid. Although it would appear reasonable that attempts to increase tissue O_2 delivery above normal levels (supranormal O_2 delivery) by means of inotropic agents, red cells, and volume expanders might be beneficial, this has not been borne out in several well controlled trials of the concept.[28,29]

Attempts to stimulate pyruvate dehydrogenase, the rate-limiting enzyme that converts pyruvic acid to acetyl-CoA (coenzyme A) for entry into the mitochondrial tricarboxylic acid cycle, with dichloroacetic acid and thus reduce pyruvate metabolism to lactic acid have not been successful, despite the compelling rationale. Although it was found that dichloroacetic acid administration reduced lactate levels and improved arterial pH in several uncontrolled trials in patients with lactic acidosis, a recent randomized controlled trial showed no mortality reduction, despite the slightly better acid-base status, in the dichloroacetic acid-treated patients.[30] The results of that trial strongly suggest that lactic acidemia per se is not the cause of death, but rather a barometer of the severity of the underlying cause.

Direct alkalinizing therapies have long been used in the treatment of metabolic acidosis, but controversy remains as to their benefit in certain forms of acidosis. Alkalinization can be accomplished by either lowering the arterial partial pressure of carbon dioxide P_{aCO_2} or administering bicarbonate or some other base equivalent. In patients struggling to lower their P_{aCO_2} to at least achieve the expected degree of hyperventilation, but at risk of respiratory muscle fatigue, assisted mechanical ventilation is indicated to meet the minimum goal of compensatory hypocapnia. Further lowering of the P_{aCO_2} may develop, especially if the patient is able to trigger the ventilator sufficiently. Whether this is acceptable will depend, of course, on the risk of adverse hemodynamic effects or barotrauma.

There is no doubt that diseases characterized by chronic metabolic acidosis have sequelae directly attributable to the acidemia and that replacement of losses and normalization of plasma bicarbonate is useful. Prevention of acidemia in renal failure, for instance, improves growth in children, increases responsiveness to erythropoietin, and reduces osteoporosis and protein wasting in adults. Furthermore, exercise tolerance is improved and dyspnea at any level of exertion is diminished. In these situations, bicarbonate can be given orally and generally in small daily amounts.

Intravenous bicarbonate is clearly indicated in the treatment of hyperkalemia either caused by a metabolic acidosis or found in association with it. Similarly, parenteral bicarbonate is beneficial with any toxin ingestion in which clearance of the toxin from inside cells and thence into the urine can be facilitated by ionic trapping in a more alkaline milieu. A good example of this principle is salicylate toxicity.[31]

Unfortunately, it is in the more severe forms of metabolic acidosis, with high rates of H^+ formation, largely the endogenous organic acid (lactic and ketoacid) acidoses, that bicarbonate and other alkalinizing agents have not shown efficacy. Thus, in situations in which the acid-base variables are most extreme and the practitioner feels most compelled to correct the values, there is no evidence to support exogenous base administration. Indeed, recent findings discussed below and several controlled trials point out the fallacy and failing of direct alkalinizing strategies. The suggestion is even raised that alkalinization may in fact be counterproductive.

The traditional reasons given to treat severe acidemia ($pH < 7.1–7.2$) are to reverse depressed catecholamine sensitivity both in the heart and peripheral vasculature, raise the threshold for cardiac arrhythmias, increase insulin sensitivity, and provide a buffer to prevent further pH declines with ongoing acid production.[32] Recently there have been several randomized trials in patients with arterial pH between 6.8 and 7.10 using sodium bicarbonate against equal amounts of sodium as NaCl in diabetic ketoacidosis and lactic acidosis. The amounts given ranged from 100 to 200 mEq over 15–30 minutes, rates roughly equivalent to or greater than the ongoing rates of acid production. The data in aggregate are consistent across all studies in showing no meaningful clinical benefit.

Studies in patients with severe diabetic ketoacidosis treated with volume repletion and insulin[33–36] show that bicarbonate does not alter the rate of hyperglycemia correction, nor does it speed the rate of normalization of arterial pH or HCO_3^- concentration. In fact, in one study, ketoacid clearance was slowed.[36] The findings in patients with lactic acidosis similarly do not support bicarbonate

use, even in the worst cases.[37–39] In those three studies, which randomized patients and used equivalent amounts of NaCl in the control groups, in general cardiac output and blood pressure were not improved, and in some instances cardiac output fell with bicarbonate. Any purported benefit to bicarbonate may simply be due to the volume-expanding effects of the accompanying sodium.

The failure of sodium bicarbonate administration in severe endogenous organic metabolic acidoses has multiple causes. It would appear that its purported benefits are outweighed by its disadvantages, some of which are better recognized than others. The better known problems include hyperosmolality, hypernatremia, hypokalemia, and post-therapeutic metabolic alkalosis.[32,40] These, however important they may be, are uncommon or minimally relevant to the acute setting of severe acidemia. Of greater and more compelling concern are the deleterious effects of alkalinization on O_2 delivery, organic acid production, uptake and metabolism by still viable tissues, cytokine and oxidant radical formation, and the fate of cells and tissue near the threshold of death.

In situations where O_2 delivery to the tissues may be marginal, acidemia aids in unloading oxygen from hemoglobin by shifting the hemoglobin-O_2 dissociation curve to the right. Reduction in the magnitude of the Bohr effect will mean that O_2 release from hemoglobin is hindered and tissue hypoxia will worsen, causing more lactic acid production. Acidosis and acidemia reduce organic acid production by virtue of simple mass action effect: that is, accumulation of product will slow the rate of any chemical reaction if all other factors are kept constant. Since the accumulation of lactate and ketoacids is a balance between their production and consumption, anything that reduces their uptake and metabolism will be disadvantageous. There is now much evidence to show that the cell membrane mechanisms (organic acid transporters) for organic acid uptake in the liver and skeletal muscle are stimulated by acidosis and inhibited by alkalosis.[13] This may help to explain the lack of any influence of bicarbonate on plasma organic acid concentration in the above cited studies.

Another concerning issue related to intravenous bicarbonate administration is the generation of CO_2. If the new CO_2 produced by reaction of HCO_3^- with H^+ ion in the central venous blood is not fully cleared by increased alveolar ventilation, then P_{aCO_2} will rise. The arterial pH will still be less acidic by virtue of some H^+ reduction, but as the arterial blood with higher P_{CO_2} reaches the peripheral tissue capillaries, the intracellular pH may decrease as the highly diffusible CO_2 moves into tissues much faster than the less diffusible charged bicarbonate ions.[41] The consequences may be transient cardiac depression or arrhythmia initiation. The phenomenon is only clinically relevant at very high rates of bicarbonate administration, such as was formerly the practice in cardiopulmonary resuscitation, when ampules of bicarbonate were pushed rapidly (within minutes) into the central circulation. In this situation the potential rate of CO_2 formation approaches 30 mmol/min and the venous P_{CO_2} could rise to several hundred mm Hg. When given by the usual slower infusion rates of 500–100 mEq over 30–60 minutes, the figure is in the range of 0.2–0.5 mmol/min. To put these figures in perspective, the normal total body CO_2 production rate is 10–12 mmol/hr.

In more severe forms of lactic acidosis, short of circulatory collapse, the ongoing rate of acid formation may be as high as 20 mmol/min, making it virtually impossible to keep pace quantitatively with bicarbonate. These rates would quickly lead to arterial hypercapnia if ventilation was not adjusted accordingly, but also to hypernatremia, volume overload, and worsened edema, if the added sodium could not be removed by forced natriuresis or hemofiltration. The only animal model to successfully employ this strategy[42] was one in which severely hypoxemic rats (fraction of inspired oxygen = 0.05) were given large amounts of glucose and bicarbonate to support normal ATP generation rates by anaerobic glycolysis alone. The result of this "bridging therapy" was to reduce mortality by 50% in the first 40 minutes. Translating this strategy to humans would mean the provision of roughly one half ampule of bicarbonate per minute and an equivalent rate of normal saline infusion of 20 L per hour.

There are two possible alternatives to $NaHCO_3$. One is Na_2CO_3 given as a 50/50 mixture with sodium bicarbonate (Carbicarb).[43] Carbicarb allows the buffering of acid without generation of CO_2 since it is the more basic CO_3 ion that is preferentially titrated to yield HCO_3^-. However, this agent has not been shown to be any more effective in experimental models of cardiac arrest than sodium bicarbonate[44,45] or other situations associated with lactic acidosis.[46–49] These results suggest that CO_2 generation with bicarbonate does not explain its lack of success. The other available alkalinizing agent that does not produce CO_2 with acid buffering is tris-hydroxymethyl aminomethane.[50] There have been no studies of its utility in severe metabolic acidosis, but the ineffectiveness of Carbicarb gives no ground to suspect it will be any better.

The most interesting and possibly chilling aspect of attempting successful alkalinization in severe metabolic acidosis ahead of resolution of the primary cause is a potential hastening and increase of cell death in marginal areas.[51] A wealth of cell and isolated organ studies in animals show that reoxygenation (whether by reperfusion or addition of oxygen to formally anoxic media) after a period of hypoxia is associated with greater cell death when the pH is normal or alkaline. When the extracellular pH is purposefully kept acidic (pH 6.6–6.8), there is much greater tissue salvage.[52–56] This pH paradox is not entirely understood, but several mechanisms may be germane. The first is that as cells become sufficiently hypoxic, they are un-

able to maintain low intracellular Ca^{2+}.[57] An acidic pH also inhibits Ca^{2+} entry into cells and thereby slows the eventual critical rise in intracellular Ca^{2+}. As calcium rises, several metabolic pathways and enzymes are stimulated, including phospholipase A,[58] that activate degradative proteases, lipases, and nucleases, causing cell necrosis. These enzymes, like most enzymes, are inhibited by acidic pH. Other possible benefits of acidosis include blunting of oxidant radical formation,[59] including NO and superoxide, in addition to inhibition of pro-inflammatory cytokine production and release by leukocytes and vascular endothelium.[60]

The concept that acidosis may be protective is provocative but obviously untested in human disease. We are moving slowly in that direction with application of permissive hypoventilation in ventilatory support and acceptance of hypercapnic respiratory acidemia. In addition to the benefits of low tidal volume, recent animal work points to additional protective effects of hypercapnia in acute lung injury.[61] Thus, for the present, there is strong justification to avoid alkalinizing agents in the critically ill, except for life-threatening hyperkalemia and toxin excretion. If the clinician feels compelled to use bicarbonate for cardiac and hemodynamic instability, then it should be given in small amounts and never as a fast infusion, and only to raise the arterial pH above 7.1.

Summary

A few general principles about metabolic acidosis should always be kept in mind. As an isolated perturbation, metabolic acidosis can be well tolerated. The company it keeps is far more the problem than the low pH value. In fact, acidosis may be somewhat protective at times when we are often most inclined to correct the acidemia directly by alkalinizing agents. Thus, the most important principle is to treat the underlying disorder generating the metabolic acidosis and resist the urge to play chemist.

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Metabolic Alkalosis

Apurv Khanna MD and Neil A Kurtzman MD

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Metabolic alkalosis is a primary pathophysiologic event characterized by the gain of bicarbonate or the loss of nonvolatile acid from extracellular fluid. The kidney preserves normal acid-base balance by two mechanisms: bicarbonate reclamation, mainly in the proximal tubule, and bicarbonate generation, predominantly in the distal nephron. Bicarbonate reclamation is mediated mainly by a Na^+-H^+ antiporter and to a smaller extent by the H^+-ATPase (adenosine triphosphate-ase). The principal factors affecting HCO_3^- reabsorption include effective arterial blood volume, glomerular filtration rate, chloride, and potassium. Bicarbonate regeneration is primarily affected by distal Na^+ delivery and reabsorption, aldosterone, arterial pH, and arterial partial pressure of carbon dioxide. To generate metabolic alkalosis, either a gain of base or a loss of acid must occur. The loss of acid may be via the gastrointestinal tract or via the kidney. Excess base may be gained by oral or parenteral HCO_3^- administration or by lactate, acetate, or citrate administration. Factors that help maintain metabolic alkalosis include decreased glomerular filtration rate, volume contraction,

hypokalemia, hypochloremia, and aldosterone excess. Clinical states associated with metabolic alkalosis are vomiting, mineralocorticoid excess, the adrenogenital syndrome, licorice ingestion, diuretic administration, and Bartter's and Gitelman's syndromes. The effects of metabolic alkalosis on the body are variable and include effects on the central nervous system, myocardium, skeletal muscle, and liver. Treatment of this disorder is simple, once the pathophysiology of the cause is delineated. Therapy consists of reversing the contributory factors that are promoting the alkalosis and, in severe cases, administration of carbonic anhydrase inhibitors, acid infusion, and low bicarbonate dialysis. *Key words: metabolic alkalosis, acid-base.* [Respir Care 2001;46(4):354–365]

Introduction

Metabolic alkalosis is a primary pathophysiologic event characterized by the gain of bicarbonate or the loss of nonvolatile acid from extracellular fluid. Alternatively, it can be defined as a primary increase in plasma bicarbonate concentration. Several authors[1,2] have reported that metabolic alkalosis is the second most common acid-base disorder in hospitalized adults, constituting around 32% of all acid-base disorders.

In order to understand this disorder, it is essential to discuss the basic mechanisms of hydrogen ion secretion and bicarbonate reabsorption by the kidney. Subsequently, the generation and maintenance of metabolic alkalosis is described, followed by a summary of the specific conditions associated with this disorder.

Renal Secretion of Hydrogen

The kidney preserves normal acid-base balance primarily by two mechanisms: reabsorption of bicarbonate, mainly by the proximal tubule (also known as bicarbonate reclamation), and acid secretion, predominantly by the distal nephron (also known as bicarbonate regeneration). In reality, there is some acid secretion in the proximal tubule and some HCO_3^- reabsorption in the distal tubule. However, for simplicity, HCO_3^- reabsorption will be assigned solely to the proximal tubule and HCO_3^- regeneration to the distal nephron.

Reabsorption of Bicarbonate

There are two main mechanisms of bicarbonate reclamation in the proximal tubule. Most reabsorption is mediated by H^+ secretion via the Na^+–H^+ antiporter localized in the brush border membrane.[3–7] Na^+-K^+-ATPase (adenosine triphosphate-ase) provides the energy for this process; hence, it is termed secondary active transport. Recent evidence also documents the presence of an H^+-ATPase accounting for a smaller portion (about a third) of HCO_3^- reabsorption.[8–12] This mechanism is primary active transport. The other primary acid transporter, the H^+-K^+-ATPase, is absent in the proximal tubule but plays a major role in distal acidification.

Figure 1 illustrates the salient features of bicarbonate reabsorption in the proximal tubule. The generation of protons results from the dissociation of carbonic acid ($H_2CO_3 \leftrightarrow H^+ + HCO_3^-$), which is formed by the hydration of CO_2 ($CO_2 + H_2O \leftrightarrow H_2CO_3$). H^+ is then secreted into the tubular lumen in exchange for Na^+, maintaining electrical neutrality, where it reacts with the filtered HCO_3^- to form H_2CO_3, which in turn dissociates into CO_2 and

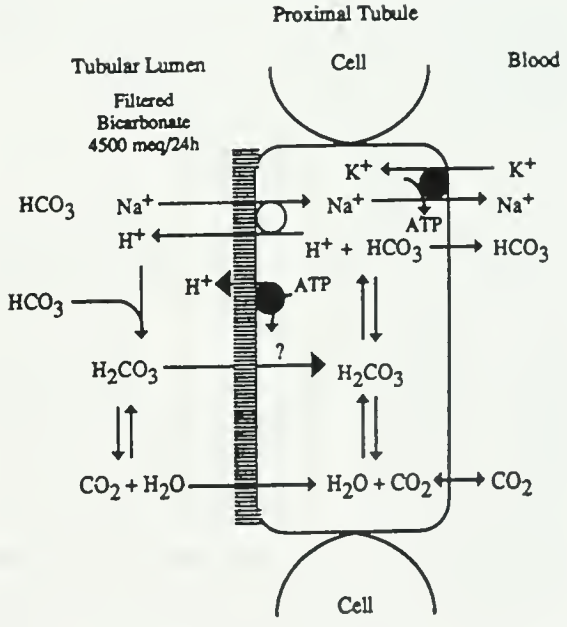

Fig. 1. Bicarbonate reabsorption in the proximal tubule. (From Sabatini S, Kurtzman NA. Metabolic alkalosis: biochemical mechanisms, pathophysiology, and treatment. In: Suki WN, Massry SG, editors. Therapy of renal diseases and related disorders, 3rd ed. Boston: Kluwer Academic Publishers; 1998:189–210, with permission.)

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H_2O.[13] Carbonic anhydrase, an enzyme found both on the luminal surface and in the cytosol of proximal tubular cells, catalyzes this dissociation. CO_2 diffuses into the tubular cell, continuing the cycle.

Na^+-K^+-ATPase, an enzyme found on the basolateral surface of proximal tubular cells,[7,14,15] provides the source of energy for H^+ secretion by the proximal tubule. The enzyme generates the electrochemical gradient for luminal Na^+ entry by maintaining a low intracellular Na^+ (approximately 12 mEq/L). Basolateral sodium exit, mediated by the activity of Na^+-K^+-ATPase, thus supplies the energy for luminal Na^+–H^+ exchange.[7,10,12,16]

Extracellular Volume

Effective arterial blood volume is the most important factor affecting HCO_3^- reabsorption in the proximal tubule.[17–19] When volume is expanded, proximal sodium reabsorption decreases as a consequence, and bicarbonate reabsorption decreases secondarily. Conversely, when volume is contracted, sodium reabsorption is increased, as is that of bicarbonate. Bicarbonate reabsorption is essentially complete in the euvolemic subject until the plasma level reaches 26 mEq/L, at which point HCO_3^- begins to appear in the urine (the bicarbonate maximum tubular rate of reabsorption [Tm]). In the volume-contracted subject, however, a Tm is not seen, and HCO_3^- reabsorption increases even at plasma values higher than 26 mEq/L. The HCO_3^- Tm defines the maximum rate of bicarbonate reabsorption observed under the particular set of conditions in which it is measured and not the maximum rate possible.

Glomerular Filtration Rate

Pitts and Lotspeich[20] first demonstrated that HCO_3^- reabsorption varied in proportion to changes in glomerular filtration rate (GFR). They noted that, at low levels of filtered load, HCO_3^- reabsorption by the kidney was complete and no HCO_3^- appeared in the urine. When the plasma HCO_3^- reached 26–28 mEq/L, no further increase in HCO_3^- reabsorptive rate occurred and HCO_3^- appeared in the urine. Several investigators have argued that the filtered load of HCO_3^- is a major determinant of the HCO_3^- reabsorption. A study by Berry and Cogan[21] in which isolated perfused proximal tubules from rabbits subjected to in vitro volume expansion (induced by changing luminal protein concentration) showed no change in HCO_3^- reabsorption, whereas salt transport was significantly reduced. This observation is in contrast to Cohen's[22] in vivo studies, which found that there was a correction of metabolic alkalosis during volume expansion when the GFR (and, hence, the filtered load of HCO_3^-) was maintained constant.

The resolution of these conflicting studies has major implications for our understanding of the forces that maintain metabolic alkalosis. If the filtered load of HCO_3^- is the major determinant of its excretory rate, then subjects with metabolic alkalosis must have a decline in the filtered load of HCO_3^-, which can only result from a decrease in GFR, since the plasma HCO_3^- is high. Correction of metabolic alkalosis would therefore best be directed toward maneuvers that increase the filtered load of bicarbonate, which would result in increased urinary excretion of bicarbonate. On the other hand, if the study by Cohen[22] is more relevant, then attention to factors other than the filtered load would be more important as regards correction.

Chloride Deficiency

Chloride deficiency stimulates bicarbonate reabsorption.[23–26] Since chloride deficiency invariably means salt depletion and, hence, contraction of extracellular volume, it is difficult to separate the effect of chloride depletion from contraction of extracellular volume on HCO_3^- reabsorption. Chloride per se does not affect the Na^+–H^+ antiporter, but it does appear to alter H^+-ATPase activity in some species.[11]

Potassium

It has been well established for many years that HCO_3^- reabsorption is inversely proportional to the level of body K^+ stores. Kurtzman et al[27] studied HCO_3^- reabsorption in 3 groups of animals: one with K^+ depletion, a second with high K^+, and a normal third group. HCO_3^- reabsorption decreased in all 3 groups following volume expansion. At any given level of fractional Na^+ excretion, HCO_3^- reabsorption was higher in K^+-depleted animals than in normal animals: K^+-loaded animals had the lowest rate of HCO_3^- reabsorption. When salt excretion was very low, and by inference volume was markedly contracted, there was no difference in bicarbonate reabsorption among the 3 groups. Micropuncture and microperfusion studies have demonstrated a direct effect of hypokalemia on the capacity of the proximal tubule to reabsorb bicarbonate.[28,29] It is likely that the effects of K^+ on H^+ ion secretion are mediated by changes in cell pH, with K^+ depletion causing intracellular acidosis and, hence, increased HCO_3^- reabsorption by stimulating the Na^+–H^+ antiporter.

Renal Acid Excretion (Bicarbonate Regeneration)

Because of dietary intake and intermediary metabolism, there is a daily production of nonvolatile acid at the rate of 1–1.5 mEq/kg body weight. This acid production results

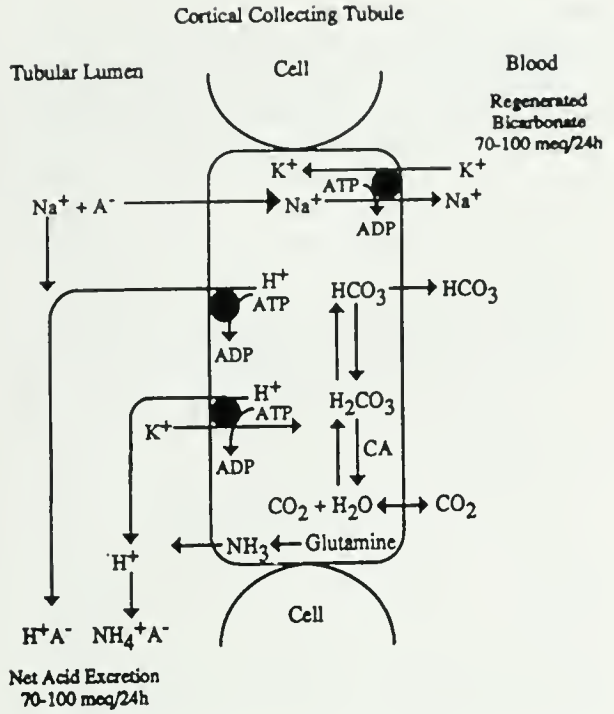

Fig. 2. Hydrogen ion secretion by the distal nephron. Electrogenic H^+ secretion (H^+-ATPase [adenosine triphosphate-ase]) and electroneutral proton secretion (H^+-K^+-ATPase) account for virtually all distal nephron acidification. (From Sabatini S, Kurtzman NA. Metabolic alkalosis: biochemical mechanisms, pathophysiology, and treatment. In: Suki WN, Massry SG, editors. Therapy of renal diseases and related disorders, 3rd ed. Boston: Kluwer Academic Publishers; 1998:189–210, with permission.)

from the metabolism of sulfoproteins and phosphoproteins. Buffers present in the extracellular fluid (mainly HCO_3^-) immediately neutralize the acids produced. The distal nephron regenerates the consumed HCO_3^- such that 70–100 mEq/d of acid is excreted, maintaining normal acid-base balance (Fig. 2).

Net acid excretion (NAE) is defined as follows: NAE = (urinary titratable acid excretion + NH_4^+ excretion) – urinary HCO_3^- excretion. Under normal conditions, 85–90% of filtered HCO_3^- is reabsorbed by the proximal tubule; hence, titratable acid and NH_4^+ excretion are formed by distal proton secretion. If the distal nephron secretes excess acid, excess HCO_3^- is regenerated, leading to metabolic alkalosis.

Titratable Acid Excretion

Titratable acid refers to the protons present in the urine in the form of weak acid anions. The most abundant buffer present in urine is phosphate (pKa [dissociation constant] = 6.8) followed by creatinine (pKa = 5.0) and urate (pKa = 5.33). According to the Henderson-Hasselbalch equation, pH = pKa + log A/HA, where A is the base and HA is a weak acid. From this equation, the pH equals the pKa when the concentration of A equals that of HA. This means that when the pH equals the pKa, 50% of the buffer is present in the ionized form and 50% is in the un-ionized form. An ideal buffer has a pKa between the blood pH and the final urine pH, so that it can accept both H^+ and OH^-. The phosphate buffer pair (pKa = 6.8) has a ratio of 1:1 (Na_2HPO_4:NaH_2PO_4) at a urine pH of 6.8. At a pH of 7.4, the ratio is 4:1, and as urine pH falls below 6.8, virtually all phosphate has been titrated and other urinary acids (creatinine, urate) assume greater importance. These other buffers may vary depending on age, sex, and diet. For example, men have higher urinary creatinine excretion (1.80 g/d) than do women (1.17 g/d). The amount of buffer present in the urine directly determines the amount of titratable acid excreted. Phosphate is the most abundant buffer in the urine. On a normal diet, its excretion is relatively constant (0.8–2 g/d), so the bulk of titratable acid is phosphate. With malnutrition and certain diets, phosphate depletion might occur, and no phosphate would appear in the urine.[30] The urine pH is the final determinant of titratable acid excretion. The lower the urine pH, the greater will be the amount of titratable acid at any one buffer concentration.

Ammonium Excretion

In the renal cell, NH_3 is formed from glutamine either from the activity of phosphate-dependent glutaminase (distal nephron) or phosphate-independent glutaminase (proximal tubule).[31,32] Because of the pKa of the NH_3:NH_4^+ pair (pKa 8.89), virtually all the NH_3 synthesized is converted to NH_4^+. In the proximal tubule, the following reaction occurs:

$$\text{Glutamine} \leftrightarrow 2\ NH_4^+ + \text{anion} \leftrightarrow HCO_3^- + 2\ NH_4^+$$

The HCO_3^- returns to the blood and NH_4^+ enters the tubular fluid via the Na^+–H^+ antiporter.[33,34] Approximately 50% of the tubular NH_4^+ is reabsorbed in the thick ascending limb. This occurs via the apical Na^+-K^+-2Cl$^-$ cotransporter, with the NH_4 substituting for K^+.

NH_4^+ accumulates in the hyperosmolar medullary interstitium. The collecting ducts do not have an NH_4^+ secretory mechanism, nor do they have substantial NH_4^+ permeability. Thus, the tiny percentage of NH_3 found in the interstitium diffuses across the tubular epithelium via nonionic diffusion into the lumen, where it is protonated.

Urine pH is a major determinant influencing NH^+ excretion. The relationship is inverse, with NH_4^+ excretion increasing as urine pH decreases. The acute changes in

excretion are related to changes in NH_3 distribution, not synthesis. More NH_3 diffuses into the tubular lumen than diffuses into the peritubular blood. If urine pH is increased acutely (eg, with bicarbonate or acetazolamide infusion), urinary NH_4^+ will dissociate, and the NH_3 then diffuses into the peritubular blood, not into the tubular lumen. K^+ depletion stimulates NH_3 production by stimulating glutamine uptake into the tubular cell.[31,35,36] K^+ deprivation of 1 week's duration also stimulates titratable acid excretion in isolated perfused rat kidney, but the importance of this finding in humans is not clear.[37]

Factors Affecting Distal Acidification

Distal Sodium Delivery

Active transport of Na^+ generates a negative potential difference in the cortical collecting tubule (CCT). This accelerates the rate of proton transport, even though H^+ secretion occurs in the absence of Na^+ transport. Thus, factors that interfere with Na^+ reabsorption, and therefore with the generation of a lumen negative potential difference, can markedly reduce the rate of distal acidification.

The influence of Na^+ transport on acidification is illustrated by the effect of the diuretic amiloride, which blocks Na^+ channels. In the turtle bladder, the drug reduces H^+ secretion only when there is a lumen negative potential difference, which it reduces to zero.[38] If the potential difference is restored to control values in the presence of amiloride, acidification returns to control values.

Since a lumen negative potential favors the secretion of K^+ as well as H^+, a defect in Na^+ transport should also be reflected by diminished K^+ secretion and hyperkalemia. All these features (sodium wastage, hyperkalemia, and metabolic acidosis), have been described in patients with obstructive uropathy and sickle hemoglobinopathies.[39–41]

The tubule's capacity to transport sodium could be affected either as a consequence of decreased distal delivery or because of aldosterone deficiency or resistance. An example of the role of decreased distal delivery is the inability of patients with severe liver disease to acidify the urine. These patients have impaired delivery of sodium to the distal nephron. Giving them either a diuretic or an infusion of sodium sulfate (both increase distal Na^+ delivery) results in a relatively normal acidification response.

Though these examples of metabolic acidosis are associated with a decrease in lumen negativity toward zero, increasing lumen negativity (by increasing Na^+ reabsorption or decreasing Cl^- reabsorption) will result in the opposite effect. H^+ and K^+ excretion will increase and hypokalemic metabolic alkalosis will ensue.

Aldosterone Excess

Aldosterone excess favors acid excretion, and is accompanied by hypokalemic metabolic alkalosis. Aldosterone deficiency is associated with hyperkalemic metabolic acidosis. Distal acidification is modulated by aldosterone through a variety of mechanisms. Aldosterone enhances both Na^+ and Cl^- reabsorption in the CCT. However, it stimulates Na^+ reabsorption more than it stimulates Cl^-. This results in increased negativity of the lumen, favoring H^+ and K^+ secretion, thus increasing the voltage-dependent component of acidification. Aldosterone also stimulates Na^+-K^+-ATPase in the CCT.[42] It also stimulates apical H^+-ATPase in the CCT and medullary collecting tubule, independent of tissue K^+ stores.[43–47] Finally, aldosterone increases renal ammoniagenesis.

In normal subjects on a high salt diet, aldosterone plays little role in maintaining acid-base or K^+ homeostasis.[48] However, in disease states like heart failure, which are characterized by a low distal delivery of Na^+, aldosterone assumes increasing importance. In this situation, aldosterone levels are high. If distal Na^+ delivery is increased by diuretic therapy, hypokalemic metabolic alkalosis may develop.

Decreased Arterial pH or Increased Arterial Partial Pressure of Carbon Dioxide

Decreased arterial pH or increased arterial partial pressure of carbon dioxide (P_{aCO_2}) results in a decrease in urine pH, to less than 5.5. The immediate response to acidemia is increased urinary titratable acid secondary to increased urinary phosphate excretion. Consequently, the kidney increases ammoniagenesis, causing ammonium excretion to rise 5–10 fold.[49] After 24 hours, CCT and medullary collecting tubule H^+-ATPase and H^+-K^+-ATPase also increase.[50] Increased ammoniagenesis excretion is the mechanism by which the kidney adapts to acidemia. By increasing the production of excretion of ammonia, the kidney can increase the acid excretion by as much as 4-fold above normal baseline.

Buffer Content

A reduction in the filtered load of phosphate, as may be seen with phosphate depletion or an increase in proximal phosphate reabsorption, results in decreased delivery of phosphate to the distal nephron. This is reflected by a decrease in titratable acid formation and a brief period of acid retention. This does not cause metabolic acidosis, because as soon as a small amount of acid is retained, ammoniagenesis is stimulated.

The other main urinary buffer is ammonia. Increased levels of aldosterone enhance ammoniagenesis, whereas the reverse is seen in its absence. Potassium also has a similar effect, with hyperkalemia inhibiting ammonia production and hypokalemia stimulating it.

Potassium

The relative contributions of aldosterone and potassium are difficult to separate because aldosterone excess is usually associated with hypokalemia, both of which stimulate ammonia production. Eiam-Ong et al[44] examined the effect of aldosterone and potassium independently on collecting tubule H^+-ATPase and H^+-K^+-ATPase activities. They postulated that the most severe metabolic alkalosis would occur when both enzymes were maximally stimulated. Experiments with 9 permutations of aldosterone (excess, normal, and deficiency states) and potassium (high, normal, and low) were designed. Only 8 permutations were performed, as it was not possible to induce hyperkalemia in the presence of hyperaldosteronism (Table 1).

Alkalemia was most severe in animals with aldosterone excess and hypokalemia. In this group, both H^+-ATPase and H^+-K^+-ATPase activities increased markedly. In the group with hyperkalemia and aldosterone deficiency, both enzymes were inhibited and acidemia occurred. If only one of those enzymes was turned on, modest alkalemia resulted. Aldosterone stimulated only the H^+-ATPase and hypokalemia stimulated only the H^+-K^+-ATPase.

In summary, acid excretion by the kidney takes place by two mechanisms. In the proximal tubule, HCO_3^- reclamation occurs as a consequence of Na^+–H^+ exchange. In the distal nephron, acid excretion occurs by the formation of titratable acid and NH_4^+ (bicarbonate regeneration). Urine pH affects the formation of both titratable acid and NH_4^+. Aldosterone is the major hormone affecting distal urinary acidification and it appears to act by stimulating the electrogenic H^+-ATPase and the Na^+-K^+-ATPase. Hypokalemia also stimulates distal urinary acidification by stimulating collecting tubule H^+-K^+-ATPase and by enhancing ammoniagenesis (Table 2).

Table 1. Effect of Body Potassium Stores and Plasma Aldosterone on Plasma Bicarbonate Concentration (in mEq/L)

Group	Low K Diet	Normal K Diet	High K Diet
Zero aldosterone	21*	20*	16**
Normal aldosterone	29*	24	22
High aldosterone	46**	29*	not done

In sham rats, plasma HCO_3 24 mEq/L
*$p = 0.05$.
**$p = 0.005$ vs sham ([44]).

To generate metabolic alkalosis, either a gain of base or a loss of acid must occur.[51] The loss of acid may be via the gastrointestinal tract, as vomitus, or via the kidneys. Normally the kidneys excrete about 100 mEq of acid daily produced as a consequence of normal protein metabolism. For each mEq of acid excreted in urine, 1 mEq of new HCO_3^- is generated and added to the blood. For metabolic alkalosis to be generated by the kidney, net acid excretion must increase, resulting in the addition of excess HCO_3^- to the blood. This is a function mainly of the distal nephron. Even if new HCO_3^- is added to the blood, metabolic alkalosis does not necessarily occur, as the kidney may excrete this excess. For sustained metabolic alkalosis to occur, the excess HCO_3^- must not be excreted; that is, the kidney must reclaim the high HCO_3^- present in the glomerular filtrate. Also, an increase in HCO_3^- reabsorptive capacity alone cannot generate metabolic alkalosis, because HCO_3^- reabsorption is normally 100% to begin with.

Aldosterone excess increases Na^+ reabsorption in the distal nephron and enhances H^+ and K^+ secretion. The increased Na^+ reabsorption results in extracellular volume expansion, which in turn depresses proximal reabsorption, thus increasing distal Na^+ delivery. Therefore, patients with primary aldosterone excess typically have metabolic alkalosis accompanied by hypokalemia.

Maintenance of Metabolic Alkalosis

Numerous factors play a role in the maintenance of metabolic alkalosis (Table 3). Glomerular filtration rate is reduced in virtually all patients with the syndrome who are volume contracted. This reduction prevents the increased HCO_3^- from being filtered. Therefore, even though the plasma HCO_3^- is increased, excretion does not rise. Hypokalemia perpetuates metabolic alkalosis by reducing the GFR. This reduction occurs because of increased renal vascular resistance.[52,53] Volume contraction may have an effect independent of filtered load to stimulate tubular HCO_3^- absorption. Potassium depletion also stimulates tubular reabsorption of HCO_3^- as a result of intracellular acidosis. Hypochloremia per se stimulates renin release, resulting in a decreased GFR.[54,55]

There may also be a role for passive HCO_3^- backflux in the maintenance of metabolic alkalosis.[56] There is an increase in HCO_3^- concentration in the proximal tubule during metabolic alkalosis. Thus, the increase in salt and water reabsorption that occurs in subjects with metabolic alkalosis, combined with the decrease in H^+ ion secretion, results in an increase in the HCO_3^- concentration of the urine in the proximal tubule. This may exceed the blood concentration, resulting in a gradient for HCO_3^- transport from the lumen to the blood. Cogan and Liu,[53] in a micropuncture study in rats following HCO_3^- loading, did

Table 2. The Generation of Metabolic Alkalosis

Generation	Examples
I. Loss of acid from extracellular space	
A. Loss of gastric fluid (HCl)	Vomiting
B. Acid loss in the urine: increased distal Na^+ delivery in presence of hyperaldosteronism	Primary aldosteronism and diuretic administration
C. Acid shifts into cells	Potassium deficiency
D. Loss of acid into stool	Congenital chloride-losing diarrhea
II. Excessive HCO_3^- loads	
A. Absolute	
1. Oral or parenteral HCO_3^-	Milk alkali syndrome
2. Metabolic conversion of the salts of organic acids to HCO_3^-	Lactate, acetate, or citrate administration (especially in conditions with underlying liver disease)
B. Relative	$NaHCO_3$ dialysis
III. Post-hypercapnic states	Correction of chronic hypercapnia in presence of low-salt diet or in a patient with congestive heart failure

(Adapted from Reference 51.)

not observe gradients high enough to result in substantial backflux, but this may occur in some models of metabolic alkalosis.

Pathophysiologic States Associated with Metabolic Alkalosis

Gastric Alkalosis

With vomiting or gastric drainage, profound metabolic alkalosis occurs (Fig. 3). This may be accompanied by marked hypokalemia and volume contraction. These changes result from mechanisms other than the loss of Na^+ and K^+ in vomitus, since there is little Na^+ and K^+ in gastric juice.

With the loss of HCl, plasma HCO_3^- rises, with little change in Na^+ and K^+. When the plasma HCO_3^- exceeds the reabsorptive capacity of the proximal tubule, HCO_3^- appears in the urine. Since it is in the form of $NaHCO_3$, some of the Na^+ is exchanged for K^+. Therefore, early in the process, there is a high urine pH, Na^+, and K^+. Chloride is lost via the vomitus. This overall loss of salt (Na^+ in the urine, and Cl^- in the vomitus) leads to volume contraction and, hence, increased proximal HCO_3^- reab-

Table 3. Factors That Maintain Metabolic Alkalosis

Factor	Proposed Mechanism
Decreased GFR	Increases fractional HCO_3^- reabsorption and prevents the elevated plasma HCO_3^- concentration from exceeding the bicarbonate maximum tubular rate of reabsorption.
Volume contraction	Stimulates proximal tubular HCO_3^- reabsorption.
Hypokalemia	Decreases GFR and increases proximal tubular HCO_3^- reabsorption; stimulates Na-independent/K-dependent (low) secretion in CCT.
Hypochloremia*	Increases renin, decreases GFR, and decreases distal chloride delivery (increases proton secretion in MCT).
Passive backflux of HCO_3^-	Creates a favorable concentration gradient for passive HCO_3^- movement from proximal tubular lumen to blood
Aldosterone	Increases Na^+-dependent proton secretion in CCT and Na-independent proton secretion in CCT and MCT

All factors decrease urinary HCO_3^- excretion in vivo.
* Animal models are associated with hypokalemia; thus, the precise role of chloride in humans is not clearly understood.
GFR = glomerular filtration rate.
CCT = cortical collecting tubule.
MCT = medullary collecting tubule.
(Adapted from Reference 17.)

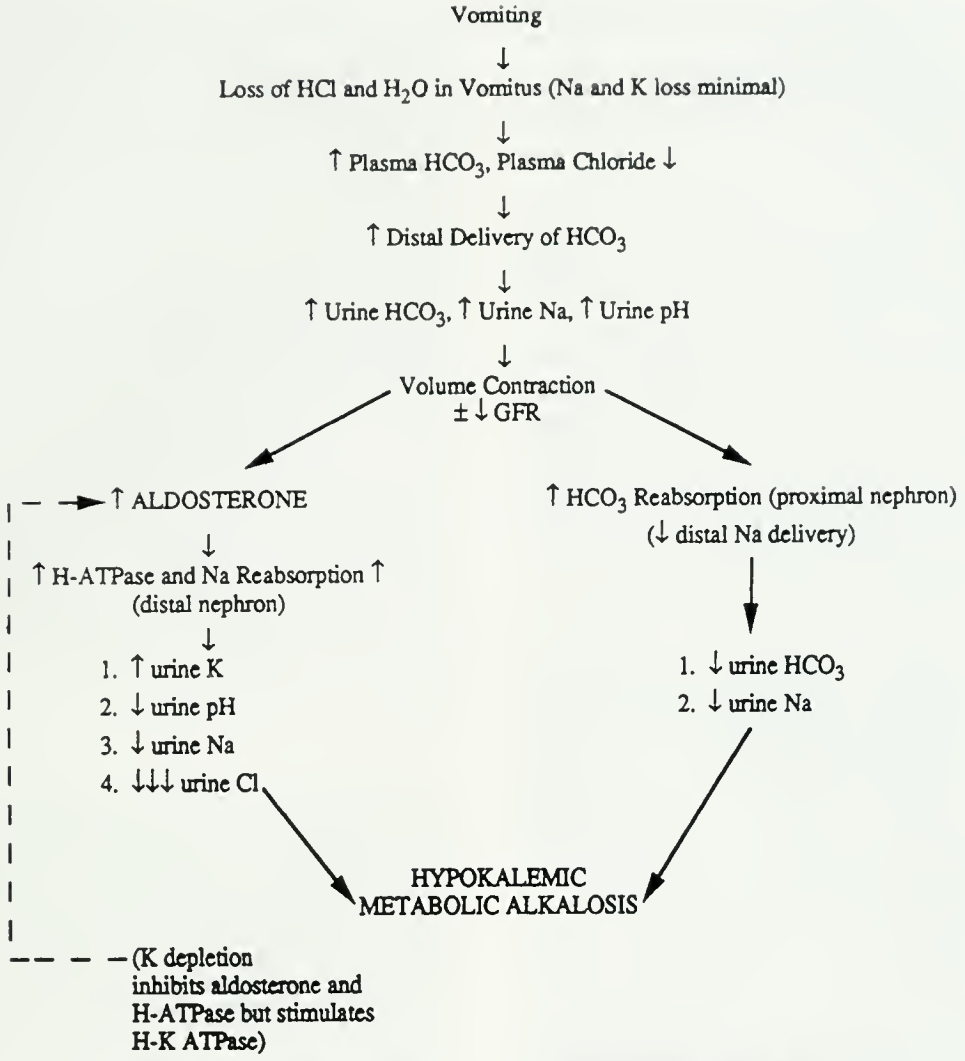

Fig. 3. Schema for the pathogenesis of gastric alkalosis. GFR = glomerular filtration rate. ATPase = adenosine triphosphate-ase. (From Sabatini S, Kurtzman NA. Metabolic alkalosis: biochemical mechanisms, pathophysiology, and treatment. In: Suki WN, Massry SG, editors. Therapy of renal diseases and related disorders, 3rd ed. Boston: Kluwer Academic Publishers; 1998:189–210, with permission.)

sorption. This serves to maintain the metabolic alkalosis. As proximal reabsorption increases, decreased amounts of HCO_3^- and Na^+ are delivered to the distal nephron. Because of volume contraction, aldosterone is stimulated. Aldosterone then stimulates increased Na^+ reabsorption and K^+ secretion. Because of decreased distal HCO_3^- delivery, urine pH decreases as the HCO_3^- disappears from the urine.

K^+ depletion inhibits aldosterone secretion, but because of the stimuli of volume contraction and hypokalemia, proximal HCO_3^- reabsorption remains high. Even though aldosterone levels are in the so-called normal range, taking into account the presence of hypokalemia, a profound hyperaldosteronism actually exists. It is important to note that urine Cl^- remains the only accurate marker of volume status in all phases of gastric alkalosis. Urine Na^+ may be an incorrect marker, since it is high early in gastric alkalosis and is low late in the disorder.

Therapy is directed toward correction of the salt, K^+, and water deficits. Urine Cl^- is used to assess volume status. Urine Cl^- concentration greater than 40 mEq/L usu-

Table 4 Urinary Electrolyte Concentrations and pH in Gastric and Diuretic-Induced Metabolic Alkalosis

	Vomiting		Diuretic Treatment
	Early	Late	
Na^+	↑	↓	↑
K^+	↑	variable	↑
Cl^-	↓	↓	↑
pH	↑	↓	↓

ally indicates that sufficient salt has been administrated (Table 4).

Mineralocorticoid Excess States

Hypertensive Disorders

Many conditions are associated with mineralocorticoid excess and metabolic alkalosis. These may be associated with high or low renin states. Hypertension may or may not be present, depending on the state of volume.

Unilateral renal artery stenosis increases renin secretion: secondary hyperaldosteronism results and metabolic alkalosis occurs as a consequence of accelerated potassium and hydrogen ion secretion. Renin-producing tumors may mimic unilateral renal artery stenosis. These include hemangiopericytomas (juxtaglomerular tumors), Wilms' tumor, renal hamartomas, and occasionally lung malignancies.

The patient with primary aldosteronism may have a unilateral adrenal adenoma, bilateral adrenal hyperplasia, or, rarely, adrenal carcinoma. These disorders are the second most common cause of secondary hypertension (seen in 1–2% of all hypertensive patients). Surgical resection of the adenoma results in complete correction. Adrenal carcinoma, usually metastatic at presentation, is associated with increased desoxycorticosterone and glucocorticoid production. The etiology of increased aldosterone is unknown in patients with bilateral adrenal hyperplasia. The disorder is heterogeneous in nature, with a subset of patients responding to spironolactone, another subset responding to dexamethasone, and a third subset being unresponsive to either.

The adrenogenital syndromes causing metabolic alkalosis are the 11 and 17-beta-hydroxylase deficiencies.[57] The defects result in high levels of desoxycorticosterone because of high ACTH levels resulting from the reduced cortisol synthesis. In 11-hydroxylase deficiency there is excess androgen synthesis, resulting in precocious puberty in boys and virilization in girls. With 17-beta-hydroxylase deficiency, both androgen and estrogen synthesis is blocked and both sexes develop primarily female characteristics. Both defects are associated with metabolic alkalosis, hypokalemia, and hypertension. Glucocorticoids are needed to reduce virilization in 11-hydroxylase deficiency, and sex hormones are required in 17-beta-hydroxylase deficiency for development of secondary sex characteristics.

Licorice ingestion (natural licorice) results in hypokalemic metabolic alkalosis. Renin and aldosterone are low. This compound impairs the action of the enzyme 11-beta-hydroxysteroid dehydrogenase that converts cortisol to cortisone in aldosterone-responsive tissues such as the collecting tubules in the kidney. Cortisol binds with equal avidity as aldosterone to the mineralocorticoid receptor and circulates in a much higher concentration; thus, cortisol would inappropriately function as a mineralocorticoid were it not converted locally by 11-beta-hydroxysteroid dehydrogenase to inactive metabolites such as cortisone. Endogenous aldosterone secretion is appropriately suppressed in this setting, which has been called the syndrome of apparent mineralocorticoid excess. In the United States the compound is present in some chewing tobaccos. A few cases characterized by spontaneous deficiency of 11-beta-hydroxysteroid dehydrogenase in the absence of licorice ingestion has also been reported. Carbenoxolone, an agent used in Europe to treat peptic ulcer disease, is similar to glycyrrhizic acid. Also nasal sprays containing 9-alpha-fluro-prednisolone, if used to excess, could result in hypertension and metabolic alkalosis.

Patients with Liddle's syndrome have hypertension and metabolic alkalosis. They behave as if they have mineralocorticoid excess, even though levels of renin and aldosterone are actually suppressed.[58] The defect is in the Na^+ channel in the distal nephron. The abnormalities can be reversed with amiloride or triamterene administration, but not by spironolactone.

Diuretic Administration

Administration of thiazides, ethacrynic acid, or furosemide is often associated with metabolic alkalosis. That this alkalosis occurs because of enhanced excretion of Na^+ and Cl^- without proportional loss of HCO_3^- (contraction alkalosis) appears simplistic. Metabolic alkalosis occurs because of excess renal acid excretion. There is increased lumen negativity because of decreased Cl^- permeability in the collecting duct and increased activity of one of the renal ATPases.

Furosemide causes metabolic alkalosis in animals.[59] If adrenalectomized animals are given diuretics and are replaced with normal amounts of aldosterone, they develop a less severe alkalosis. The hypokalemia that ensues stimulates H^+-K^+-ATPase activity. These animals do not get increased levels of H^+-ATPase because they cannot develop hyperaldosteronism. When an H^+-K^+-ATPase inhibitor was given to steroid-replete adrenalectomized animals treated with diuretics, bicarbonate concentration decreased to normal. These data demonstrate that diuretic-induced alkalosis requires activation of both the H^+-ATPase and the H^+-K^+-ATPase. The former is caused by increased levels of aldosterone, whereas the latter is the consequence of hypokalemia.

The effects of loop diuretics mimic Bartter's syndrome. There is decreased reabsorption of Na^+, K^+, and Cl^- in the loop of Henle. This leads to volume contraction and hypokalemia; renin and aldosterone secretion increase. Elevated aldosterone leads to further K^+ loss and increased H^+ secretion in the collecting duct. The K^+ depletion stimulates renal H^+-K^+-ATPase activity. Loop diuretic

administration is distinguished from Bartter's syndrome by testing the urine for diuretics. Thiazide diuretics mimic the effects of Gitelman's syndrome. This syndrome is characterized by renal magnesium wasting, inducing renal K^+ loss and alkalosis, and is due to a defect in the neutral NaCl transporter in the distal tubule.

Bartter's Syndrome

This syndrome is associated with metabolic alkalosis and low to normal blood pressure. It has been suggested that this syndrome represents a form of salt wastage due to defective reabsorption of NaCl in the loop of Henle.[60,61] The salt wastage contracts plasma volume, which stimulates renin and aldosterone secretion. As loop K^+ reabsorption is also impaired, adrenalectomy does not correct this defect. Metabolic alkalosis results from K^+ depletion and mineralocorticoid excess. The state is maintained because of enhanced proximal reabsorption secondary to contracted plasma volume and hypokalemia. Therapy of such patients is difficult, with massive amounts of potassium needed to even partially correct hypokalemia. In addition, hypomagnesemia is often present.

Gitelman's Syndrome

This syndrome is rarer than Bartter's syndrome. It is usually diagnosed in late childhood or early adulthood. The primary defect in this disorder is the neutral NaCl transporter in the distal tubule. The defect causes hypomagnesemia, renal K^+ loss, and metabolic alkalosis. Renin and aldosterone are high, as in Bartter's syndrome. Patients with Gitelman's syndrome respond to furosemide but not thiazides. The reverse is seen in patients afflicted with Bartter's syndrome.

Congenital Chloride-Losing Diarrhea

Patients with this rare disease have hypochloremia, a high stool Cl^- concentration, and an absence of Cl^- in the urine. The stool Cl^- concentration is higher than the sum of Na^+ and K^+ concentrations. These patients probably have a defect in Cl^-/HCO_3^- transport in the colon and ileum and are unable to transport Cl^- against an electrochemical gradient. This defect results in the loss of Cl^- and acid in the stool, which causes metabolic alkalosis. Volume contraction stimulates the renin-angiotensin-aldosterone axis, resulting in loss of K^+ from the urine as well as the stool. These patients do not respond to antidiarrhea medication, making therapy difficult.

Posthypercapnic Metabolic Alkalosis

Chronic hypercapnia enhances acid and chloride excretion. In the distal nephron there is increased H^+-ATPase activity (in the CCT and medullary collecting tubule).[62] Chronic hypercapnia also stimulates proximal bicarbonate reabsorption, maintaining an increased concentration of plasma HCO_3^-. Following the return of P_{CO_2} to normal, there is usually retention of Cl^- and loss of HCO_3^- in the urine. If patients with hypercapnia are on a low-salt diet or are treated with diuretics so that volume is contracted, proximal reabsorption will be enhanced and HCO_3^- reabsorption will remain elevated following the return of P_{CO_2} to normal, resulting in posthypercapnic metabolic alkalosis.

If this type of alkalosis occurs in the setting of volume depletion, it is corrected by salt administration. However, if post hypercapnic metabolic alkalosis occurs in a state of effective volume depletion, such as in congestive heart failure, treatment differs markedly. In this setting, salt administration is contraindicated and treatment is directed toward improving cardiac function.

Respiratory Compensation

Metabolic alkalosis may lead to compensatory hypoventilation and consequent CO_2 retention. Uncomplicated metabolic alkalosis is usually not associated with profound alveolar hypoventilation. P_{CO_2} is usually not higher than 55 mm Hg. Levels higher than this suggest coexistent pulmonary disease.

Effects of Metabolic Alkalosis

Metabolic alkalosis affects the central nervous system in a variety of ways. Cerebral blood flow decreases, lethargy and confusion may occur, and if alkalemia is severe, coma and seizures may occur. The respiratory center may be depressed, thereby decreasing the drive for alveolar ventilation. The respiratory response to hypercapnia is also blunted. This may be a problem in patients with chronic pulmonary disease. Neuromuscular irritability can occur and is manifested by muscle twitching, spasm, and tetany. Positive Chvostek's and Trousseau's signs may be present and are probably related to the decreased ionizable calcium seen in alkalemia.

In animal studies,[63] alkaline pH decreased aldosterone release in response to angiotensin II. Alkalemia also decreases myocardial contractility in vitro, as well as blunts the inotropic response to norepinephrine.[64] These findings are probably the result of decreased cytosolic calcium. The effect of metabolic alkalosis on cardiac function in humans is not well understood. Initially a small inotropic effect occurs, probably the result of increased peripheral vascular resistance. With time, because of alterations in cytosolic calcium, myocardial contractility is depressed. Electrocardiographic changes include Q-T prolongation and U waves, as well as atrial and ventricular arrhythmia.

Diuretics may precipitate hepatic coma because they cause hypokalemic metabolic alkalosis. In this condition there is extracellular alkalosis but also intracellular acidosis because of the movement of K^+ out of cells, and H^+ into cells. Thus, more NH_3 is formed outside the cell and then diffuses into the cell, where it is converted to NH_4^+. NH_4^+ is nondiffusable and thus is trapped inside the cell, causing toxicity.

Hypokalemia and hypomagnesemia frequently coexist with metabolic alkalosis. Hypokalemia is associated with abnormalities in the electrical properties of the heart and muscle; muscle blood flow decreases because of vasoconstriction, and there are abnormal responses to a variety of hormones and drugs. Hypokalemia also causes a renal concentrating defect and stimulates NH_4^+ production, further worsening the alkalemia.

Therapy of Metabolic Alkalosis

Once the pathophysiology of the type of metabolic alkalosis is delineated, the treatment is simple. If volume contraction is the underlying mechanism, it should be restored to normal. Potassium and magnesium deficits should be corrected. Primary mineralocorticoid excess may be antagonized with spironolactone prior to definitive therapy. Carbonic anhydrase inhibition, acid administration, and hemodialysis using an acid bath may be used on rare occasions to treat the disorder. In patients with posthypercapnic metabolic alkalosis, acetazolamide will result in prompt bicarbonate diuresis if volume status is normal. However, in patients with contraction of effective volume, the effect of this diuretic may be blunted and its use may make the patient worse .

Infusion of a dilute solution of hydrochloric acid (NH_4Cl or arginine hydrochloride) into a large central vein over 18–24 hours may be done in selected cases. However, NH_4Cl is contraindicated in patients with hepatic failure, and both NH_4Cl and arginine hydrochloride worsen azotemia in renal failure.

If HCl is infused, concentrations of 100–200 mEq/L should be used. To calculate the amount needed, initial estimates should assume a distribution in only the extracellular space (20% of body weight). The true space of distribution is ultimately closer to 50% of body weight. pH and P_{CO_2} should be measured frequently.

In patients with renal failure or precarious fluid status, dialysis against a high-Cl /low-HCO_3^- may help. Hemodialysis allows more precise regulation of fluids compared to peritoneal dialysis.

The therapeutic modalities just described (ie, acid infusion or dialysis and carbonic anhydrase inhibitors) have very specific and limited indications and may be very hazardous when improperly applied. Their use should be reserved for the physician who is an expert in the management of renal disease and acid-base disturbances.

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Respiratory Acidosis

Scott K Epstein MD and Nirupam Singh MD

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Respiratory acidosis, or primary hypercapnia, is the acid-base disorder that results from an increase in arterial partial pressure of carbon dioxide. Acute respiratory acidosis occurs with acute (Type II) respiratory failure, which can result from any sudden respiratory parenchymal (eg, pulmonary edema), airways (eg, chronic obstructive pulmonary disease or asthma), pleural, chest wall, neuromuscular (eg, spinal cord injury), or central nervous system event (eg, drug overdose). Chronic respiratory acidosis can result from numerous processes and is typified by a sustained increase in arterial partial pressure of carbon dioxide, resulting in renal adaptation, and a more marked increase in plasma bicarbonate. Mechanisms of respiratory acidosis include increased carbon dioxide production, alveolar hypoventilation, abnormal respiratory drive, abnormalities of the chest wall and respiratory muscles, and increased dead space. Although the symptoms, signs, and physiologic consequences of respiratory acidosis are numerous, the principal effects are on the central nervous and cardiovascular systems. Treatment for respiratory acidosis may include invasive or noninvasive ventilatory support and specific medical therapies directed at the underlying pathophysiology. *Key words: respiratory acidosis, acid-base, acidosis, alkalosis, hypercapnia, hypoventilation, respiratory muscles.* [Respir Care 2001;46(4):366–383]

Introduction

Arterial partial pressure of carbon dioxide (P_{aCO_2}) is tightly regulated under normal conditions and kept within a fairly narrow range (37–43 mm Hg at sea level). Although arterial partial pressure of oxygen (P_{aO_2}) decreases with increasing age, P_{aCO_2} appears to remain unaltered from the age of 3 onwards.[1] Respiratory acidosis, or primary hypercapnia, is the acid-base disorder that results from an increase in P_{aCO_2} to more than 43 mm Hg. At altitude the normal range of P_{aCO_2} is lower because of chronic hyperventilation resulting from hypoxia. Therefore, at 13,000 feet a P_{aCO_2} of 40 mm Hg would actually represent substantial hypercapnia.[2] Whenever CO_2 excretion from the lungs fails (usually from alveolar hypoventilation) to match the body's CO_2 production, respiratory acidosis results. Acute respiratory acidosis occurs with acute (Type II) respiratory failure that may result from any sudden respiratory parenchymal, airways, pleural, chest wall, neuromuscular or central nervous system (CNS) event (Table 1). It is characterized by a rapid increase in P_{aCO_2} with minimal increase in plasma bicarbonate and a large decrease in pH. Chronic respiratory acidosis is typified by a sustained increase in P_{aCO_2}, resulting in renal adaptation and a more marked increase in plasma bicarbonate (Table 2). Respiratory acidosis must be carefully distinguished from secondary hypercapnia, in which the elevated P_{aCO_2} results from hypoventilation as a response to metabolic alkalosis.[3]

Pathophysiology of Respiratory Acidosis

In respiratory acidosis, the chemical equilibrium between bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3),

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \quad (1)$$

is disrupted, leading to the acidification of body fluids or an increase in hydrogen ion concentration ($[H^+]$).[4] The relationship between P_{CO_2}, HCO_3^-, and pH can be represented using a Davenport diagram (Fig. 1), the Henderson-Hasselbalch equation (Equation 2a), or the Henderson equation (Equation 2b).

$$pH = 6.1 + \log[HCO_3^-]/(0.03 \times P_{CO_2}) \quad (2a)$$

$$[H^+] = k\, P_{CO_2}/HCO_3^- \quad (2b)$$

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As can be seen from Equations 2a and 2b, an increase in P_{aCO_2} in the absence of an increase in HCO_3^- results in an increase in H^+ (ie, a decrease in pH). With acute hypercapnia (acute respiratory acidosis) there is a rapid (over 5–10 min) but small increase in plasma bicarbonate that results from the titration of nonbicarbonate body buffers.[4] The buffers (Buf), which are predominantly cellular, combine with H^+ derived from the dissociation of carbonic acid, thereby generating bicarbonate:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$$
$$Buf^- + H_2CO_3 \rightarrow HBuf + HCO_3^- \quad (3)$$

The consequence is an increase of approximately 0.1 mEq/L of bicarbonate for each 1 mm Hg increase in P_{aCO_2}.[5] This constrains the increase in $[H^+]$ to approximately 0.75 nEq/L for each 1 mm Hg increase in P_{aCO_2}. Nevertheless, the ratio of P_{aCO_2} to HCO_3^- increases substantially, resulting in a large decrease in pH (acute respiratory acidosis) (Fig. 2). For example, an acute increase in P_{aCO_2} from 40 to 80 mm Hg, will result in an acute increase in bicarbonate, from 24 to 28 mEq/L, and a pH of approximately 7.12. Adrogué and Madias have demonstrated in an experimental animal model that the pre-existing bicarbonate level influences the magnitude of the bicarbonate change seen with acute hypercapnia.[6,7] In the setting of hypobicarbonatemia (eg, as may occur with either metabolic acidosis or chronic respiratory alkalosis), the bicarbonate increase in response to acute hypercapnia is magnified. In contrast with preexisting hyperbicarbonatemia (eg, as may occur with either metabolic alkalosis or chronic respiratory acidosis), the bicarbonate increase in response to acute hypercapnia is blunted. One additional consequence of hypercapnia is a substantial decrease in P_{aO_2} (hypoxemia), as predicted by the alveolar air equation (Equation 4),

$$P_{AO_2} = (F_{IO_2})(P_B - P_{H_2O}) - (P_{ACO_2}/R) \quad (4)$$

wherein P_{AO_2} is the alveolar oxygen tension, F_{IO_2} is the fraction of inspired oxygen, P_B is the barometric pressure, P_{H2O} is the water vapor pressure, P_{ACO_2} is the alveolar carbon dioxide tension, and R is the respiratory quotient. Under most circumstances P_{ACO_2} is essentially equal to P_{aCO_2}. The P_{AO_2} determines the maximum P_{aO_2}, so a decrease in P_{AO_2} will always result in a decrease in P_{aO_2}. Because life-threatening manifestations occur when P_{aO_2} acutely decreases to 40 mm Hg, the maximum P_{aCO_2} seen during acute hypercapnia is in the range of 80–90 mm Hg (assuming the patient is breathing room air, F_{IO_2} 0.21). One additional consequence of severe hypoxemia is lactic (metabolic) acidosis, which can further lower the pH. When

Table 1. Causes of Acute Respiratory Acidosis

Acute central nervous system depression
• Drug overdose (benzodiazepines, narcotics, barbiturates, propofol, major tranquilizers)
• Head trauma
• Cerebrovascular accident
• Central nervous system infection (encephalitis)
Acute neuromuscular disease
• Guillain-Barré syndrome
• Spinal cord injury
• Myasthenic crisis
• Botulism
• Organophosphate poisoning
Acute airways disease
• Status asthmaticus
• Upper airway obstruction (laryngospasm, angioedema, foreign body aspiration)
• Exacerbation of chronic obstructive pulmonary disease
Acute parenchymal and vascular disease
• Cardiogenic pulmonary edema
• Acute lung injury
• Multi-lobar pneumonia
Massive pulmonary embolism
Acute pleural or chest wall disease
• Pneumothorax
• Hemothorax
• Flail chest

Table 2. Causes of Chronic Respiratory Failure

Central sleep apnea
Primary alveolar hypoventilation
Obesity hypoventilation syndrome
Spinal cord injury
Diaphragmatic paralysis
Amyotrophic lateral sclerosis
Myasthenia gravis
Muscular dystrophy
Multiple sclerosis
Poliomyelitis
Hypothyroidism
Kyphoscoliosis
Thoracic cage disease
Chronic obstructive pulmonary disease
Severe chronic interstitial lung disease

supplemental oxygen is given (eg, increased F_{IO_2}) there is the opportunity for more severe hypercapnia to develop.

With a persistent increase in CO_2 tension (chronic hypercapnia or chronic respiratory acidosis), there is an up-regulation of Na^+–H^+ antiporter of the renal brush-border enzymes.[8] Increased acid excretion in respiratory acidosis is mediated by an increase in distal H^+ secretion.[5,9–15] With renal adaptation to chronic hypercapnia, the $[H^+]$ increases approximately 0.3 nEq/L for each 1 mm Hg increase in P_{aCO_2}.[16] Therefore, under these circumstances the ratio of P_{aCO_2} to HCO_3^- returns toward normal (eg, compensated respiratory acidosis), resulting in only a mild to moderate reduction in pH (see Fig. 2). In addition, chloride depletion occurs because there is increased chloride excretion (chloruresis) and a shift of chloride ions into red blood cells.[4] This adaptation is usually complete by 3–5 days and results in hypochloremic hyperbicarbonatemia (Fig. 3). Interestingly, the renal response to chronic hypercapnia is minimally affected by dietary chloride restriction.[16] Yet unless adequate chloride is supplied, plasma bicarbonate may remain markedly elevated after the chronic hypercapnic state has resolved. This can culminate in a post-hypercapnic alkalosis, an acid-base state that may be confused with metabolic alkalosis. Post-hypercapnic alkalosis is typically treated with either chloride replacement (usually as the potassium salt) or with acetazolamide (Diamox).

Although respiratory acidosis is usually associated with hypercapnia, it is important to realize that it can also be present in the setting of apparent eucapnia or hypocapnia. Normal children under the age of 3 years will have P_{aCO_2} in the range of 33–37 mm Hg. During pregnancy, particularly in the third trimester, P_{aCO_2} typically resides at 28–32 mm Hg, as a result of hormonally mediated hyperventilation. Under either of these conditions an increase in P_{aCO_2} (ie, respiratory acidosis) may be associated with P_{aCO_2} values that are still below 43 mm Hg. Another example is the coexistence of a metabolic acidosis and a respiratory acidosis (eg, a mixed acid-base disturbance). For example, in pure diabetic ketoacidosis, a bicarbonate of 10 mEq/L should result in a P_{aCO_2} of 22 mm Hg (and a pH of 7.27). If a concomitant respiratory acidosis is present, P_{aCO_2} will increase above 22 mm Hg but may still reside in a range typically considered hypocapnic.

Mechanisms of Hypercapnia and Respiratory Acidosis

P_{aCO_2} is directly proportional to the production of CO_2 ($\dot{V}_{CO_2}$) and inversely proportional to the alveolar ventilation ($\dot{V}_A$), which determines CO_2 elimination.

$$P_{aCO_2} = k\dot{V}_{CO_2}/\dot{V}_A \quad (5)$$

The constant k is equal to 0.863 mm Hg when CO_2 production is expressed in mL/min (dry gas, standard temperature and pressure) and the $\dot{V}_A$ is expressed as L/min (saturated gas, body temperature and pressure).[17] The $\dot{V}_A$ is the part of the total minute ventilation ($\dot{V}_E$) that reaches the gas exchange surfaces of the lung. The fraction of gas not reaching the gas exchange surfaces is "wasted" and is referred to as the dead space volume. The term V_D/V_T (dead space/tidal volume) refers to the proportion of each

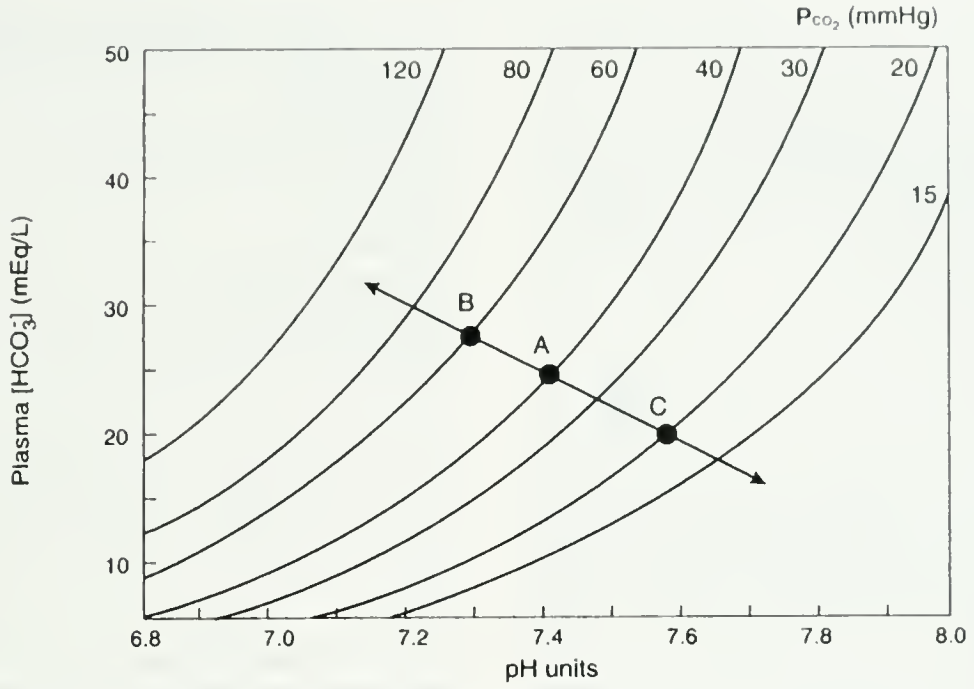

Fig. 1. Davenport diagram. Plots of plasma bicarbonate concentration ([HCO_3^-]) versus blood pH at various arterial partial pressure of carbon dioxide (P_{CO_2}) values. Point A represents the normal state, with P_{CO_2} of 40 mm Hg, HCO_3^- of 24 mEq/L, and pH of 7.40. A buffer line (BAC) shows the response to either an increase (Point B) or a decrease (Point C) in P_{CO_2}. (From Criner GJ, D'Alonzo GE. Pulmonary pathophysiology. Lindell, PA: Fence Creek; 1999:81, with permission.)

V_T breath that goes to ventilating the dead space. Therefore, the denominator of Equation 5 can be rearranged to yield Equation 6.

$$P_{aCO_2} = k\dot{V}_{CO_2}/\dot{V}_E(1 - V_D/V_T) \quad (6)$$

Based on Equations 5 and 6, it becomes evident that hypercapnia can result from an increase in CO_2 production, a decrease in $\dot{V}_A$ (either decreased total $\dot{V}_E$ or increased V_D/V_T ratio), or both. In each of these cases, CO_2 elimination is exceeded by CO_2 production, leading to an increase in CO_2 tension. That stated, the overwhelming

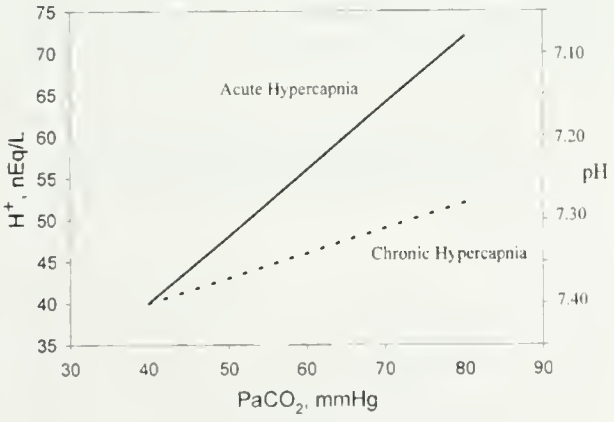

Fig. 2. Relationship between arterial partial pressure of carbon dioxide (P_{aCO_2}), concentration of hydrogen ions ([H^+]), and pH in acute and chronic hypercapnia.

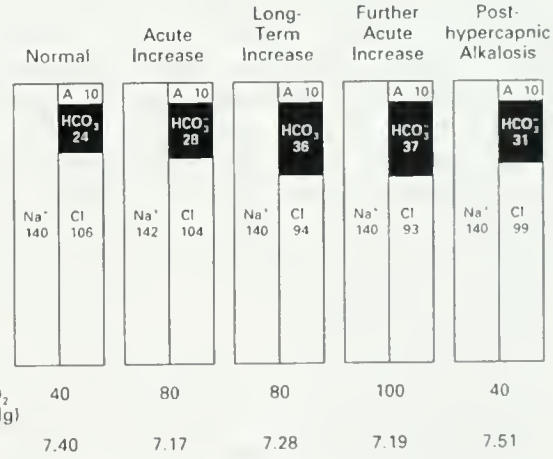

Fig. 3. Changes in acid-base and electrolytes occurring at various stages of respiratory acidosis. P_{aCO_2} = arterial partial pressure of carbon dioxide. A^- = unmeasured plasma anions. Cl^- = plasma chloride. Na^+ = plasma sodium. HCO_3^- = plasma bicarbonate. (From Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. First of two parts. N Engl J Med 1998;338(1): 26–34, with permission.)

majority of cases of respiratory acidosis result from alveolar hypoventilation.

Increased Carbon Dioxide Production. Carbon dioxide is a by-product of the body's metabolic processes, adding a substantial amount of acid to the circulation, which must be excreted by the lungs and the kidneys to prevent the development of acidosis. An increase in CO_2 production can result from numerous processes, including exercise,[18] fever,[19] sepsis,[20,21] burns,[20–23] thyrotoxicosis,[24] and catabolic states such as multi-organ failure.[25] For example, with each degree of temperature elevation above normal, CO_2 production increases by approximately 13%.[17] Therefore, to maintain a normal P_{aCO_2} in the setting of a fever to 40° C, $\dot{V}_A$ must be increased by approximately 40%. Nutrition also affects $\dot{V}_{CO_2}$ and depends both on the respiratory quotient (the ratio of CO_2 production to O_2 consumption) of the ingested nutrients and the total caloric intake. For example, the respiratory quotient of carbohydrate is 1, that of fat is 0.8, and that of protein is 0.7. When calories are given in excess of the energy needs, these are converted in the body to fat (lipogenesis), increasing the respiratory quotient to approximately 8.0.

Although excess CO_2 production alone might lead to hypercapnia, this rarely occurs. In health, an increase in $\dot{V}_{CO_2}$ is usually matched by an increase in CO_2 elimination. For example, in the presence of a normal respiratory system, $\dot{V}_A$ increases to keep P_{aCO_2} within the normal range when $\dot{V}_{CO_2}$ increases as a result of high fever, carbohydrate loading, or vigorous exercise. In contrast, in patients with respiratory diseases that limit ventilatory capacity, $\dot{V}_A$ may be inadequate to eliminate excess CO_2, and hypercapnia with overt respiratory failure can result.[26] In stable chronic obstructive pulmonary disease (COPD), a carbohydrate-rich meal will increase $\dot{V}_{CO_2}$ and total $\dot{V}_E$ and reduce exercise capacity, compared to an isocaloric fat-rich preparation.[27] Another example is during mechanical ventilation, wherein heavy sedation or neuromuscular blockade prevents the patient from increasing $\dot{V}_E$ in response to increased CO_2 production.[28] One additional clinical consequence of overfeeding and the resultant hypercapnia is failure to wean from mechanical ventilation.[29,30]

Alveolar Hypoventilation. In the setting of normal or elevated CO_2 production, a decrease in $\dot{V}_A$ will result in hypercapnia. Reduced $\dot{V}_A$ can result from either a decrease in total $\dot{V}_L$ (the product of respiratory rate and V_T) or abnormal ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships in the lung. A decrease in total $\dot{V}_E$ (sometimes referred to as global hypoventilation) will result in hypercapnia and respiratory acidosis. In this condition, although CO_2 is delivered to the lung, ventilation is inadequate for satisfactory CO_2 elimination. This results in an increase in alveolar CO_2 and, consequently, P_{aCO_2}. This state is also characterized by hypoxemia with a normal alveolar-arterial oxygen gradient ($P(A\text{-}a)O_2$). Global hypoventilation can result from either a decrease in respiratory drive ("won't breathe") (Table 3) or a reduction in respiratory muscle or chest wall function ("can't breathe") (Table 4).

Table 3. Causes of Global Hypoventilation Resulting from Decreased Central Drive (Won't Breathe)

General anesthesia
Sedatives
Central sleep apnea/obesity hypoventilation syndrome
Primary alveolar hypoventilation
Cerebral edema
Central nervous system infection (encephalitis)
Cerebrovascular accident
Central nervous system trauma
Hypothyroidism
Brain stem lesions (sarcoid, medullary infarction)

Abnormal Ventilatory Drive. Under normal circumstances an increase in P_{aCO_2} leads to a marked and predictable increase in central respiratory drive. In contrast, central hypoventilation, a manifestation of abnormal ventilatory control, is characterized by an inappropriately low drive despite the presence of hypercapnia.[17,31–35]

The central respiratory controller resides in the medulla and receives afferent input from nearby chemoreceptors and from a number of peripheral receptors. The central controller also receives input from the pons and from a behavioral control center in the cerebral cortex. Two components of the controller, the dorsal respiratory group and the ventral respiratory group, send efferent output to the diaphragm and accessory respiratory muscles, respectively.[36] Stimulation of central chemoreceptors (located in the medulla) provides the principal response to hypercapnia and acidosis, resulting in an increase in the frequency of the respiratory rhythm.[37] These receptors respond primarily to changes in the hydrogen ion concentration and partial pressure of carbon dioxide (P_{CO_2}) in the cerebrospinal

Table 4. Causes of Global Hypoventilation Resulting from Decreased Respiratory Pump Function (Can't Breathe)

Chest wall disorders
Kyphoscoliosis
Thoracoplasty
Obesity
Respiratory muscle weakness
• Spinal cord (cervical spine injury)
• Anterior horn cell (amyotrophic lateral sclerosis)
• Phrenic nerve (Guillain-Barré syndrome)
• Neuromuscular junction (myasthenia gravis)
• Myopathy (polymyositis)

fluid and medullary interstitial fluid. An increase in P_{aCO_2} or $[H^+]$ stimulates respiration, whereas a decrease in P_{aCO_2} or $[H^+]$ inhibits ventilation. CO_2 is lipid soluble and is highly and rapidly permeable across the blood-brain barrier. In contrast, hydrogen ions penetrate the blood-brain barrier much more slowly and, hence, the effect on ventilation is slower and smaller.[38]

The principal peripheral chemoreceptors are the carotid bodies. These receptors are located at the bifurcation of the carotid arteries, are capable of sensing changes in P_{aO_2}, and are responsible for about 90% of the ventilatory response to hypoxemia (increase in $\dot{V}_E$).[37] The carotid bodies appear to play a lesser role in the response to hypercapnia and acidosis.[39] Resection of the carotid bodies leads to an increase in resting P_{aCO_2} by 2–4 mm Hg, secondary to a reduction in the $\dot{V}_A$.[40]

An important influence on respiratory drive is the level of CNS arousal. During non-REM sleep the ventilatory response to P_{aCO_2} is blunted. $\dot{V}_E$ decreases, primarily because of a reduction in V_T. The result is an increase in P_{aCO_2} by 3–10 mm Hg.[36] In addition, REM sleep is characterized by inhibition of spinal motor neurons to all respiratory muscles other than the diaphragm. The consequence of these sleep-related changes is a substantial worsening of respiratory acidosis in patients with pre-existing hypercapnia, especially those with diaphragmatic dysfunction. Studies have also indicated that sleep deprivation decreases the ventilatory response to hypercapnia.[41] More recently, a study of normals, conducted under strictly controlled behavioral and environmental conditions, found that sleep deprivation failed to reduce either the sensitivity of central chemoreceptors or the resting $\dot{V}_E$.[42]

Abnormalities of the Chest Wall and Respiratory Muscles. Global hypoventilation can also result from disorders of the chest wall or respiratory muscle pump. In these instances respiratory drive is often elevated but ineffective, either because the resulting total $\dot{V}_E$ is insufficient to match the resistive or elastic loads placed on the respiratory system or because of the impact of rapid shallow breathing on $\dot{V}_A$. Disorders of the CNS (upper motor neuron), spinal cord, anterior horn cells (lower motor neuron), phrenic nerves, neuromuscular junction, or the respiratory muscles themselves can all be associated with either acute or chronic hypercapnia.[43]

Increased Dead Space. Ventilation-perfusion matching is important not only for oxygenation but also for maintaining eucapnia.[44] CO_2 must be delivered to the lung (perfusion, $\dot{Q}$) to be effectively eliminated through ventilation ($\dot{V}$). Therefore, CO_2 elimination decreases when perfusion to an alveolar segment is reduced. This fact is often not appreciated when the respiratory controller and respiratory muscle pump are functional, because an increase in total $\dot{V}_E$ can compensate and keep P_{aCO_2} within the normal range.[17]

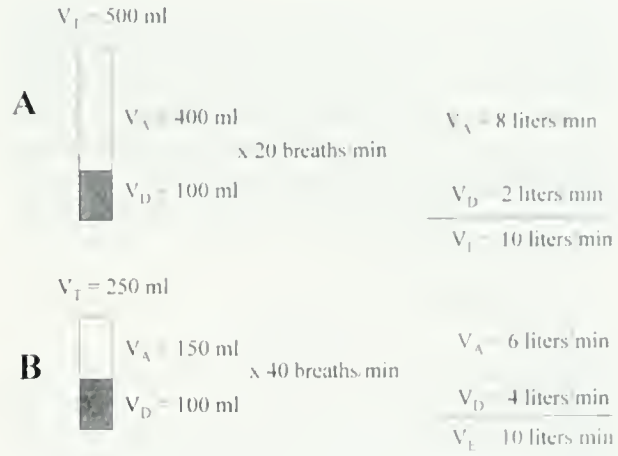

Fig. 4. Influence of change in breathing pattern on alveolar ventilation (V_A). Total minute ventilation (V_E, the product of respiratory frequency and tidal volume [V_T]) remains unchanged in going from condition A to condition B. In condition B, a rapid shallow breathing pattern leads to an increase in dead space ventilation (V_D) and a decrease in alveolar ventilation.

Areas of lung that are ventilated but inadequately perfused (ie, wasted ventilation) can be collectively represented by the V_D/V_T ratio, or the amount of wasted volume per breath. In health, V_D/V_T is approximately 0.25–0.35 in the sitting position and is principally composed of the anatomic dead space (the volume of the conducting airways from the trachea to the terminal bronchioles). Since this is a fixed anatomic volume, increasing the V_T will reduce the percentage of dead space ventilation. Conversely, an increase in respiratory rate with a decrease in V_T (the rapid shallow breathing pattern found in many respiratory diseases) will increase the proportion of dead space ventilation (Fig. 4). At a fixed total $\dot{V}_E$, a shift to a more rapid and shallow breathing pattern will lead to hypercapnia and respiratory acidosis. This pattern of breathing is often present during acute respiratory failure (ARF) and during failure to wean from mechanical ventilation.[45,46] The anatomic dead space (in mL) can be approximated by the patient's ideal body weight in pounds. In disease states associated with $\dot{V}/\dot{Q}$ mismatching, there may be alveolar units with minimal or no perfusion and that are, therefore, incapable of effectively eliminating CO_2 (ie, wasted ventilation or dead space). In these pathological states, the dead space is referred to as the "physiologic dead space," a value that includes the anatomic dead space. Because of the shape of the CO_2 dissociation curve, hyperventilation of other alveoli can effectively compensate and keep P_{aCO_2} normal. If other alveolar units cannot be effectively hyperventilated to increase CO_2 elimination, an elevated dead space will result in hypercapnia and respiratory acidosis. Causes of an increase in dead space include pulmonary

embolism, pulmonary vascular disease with remodeling and obliteration of pulmonary vessels, pulmonary capillary compression from hyperinflation or positive pressure ventilation, and destruction or obliteration from pulmonary parenchymal diseases such as emphysema or pulmonary fibrosis. Any process that causes severe pulmonary hypoperfusion also has the potential to reduce CO_2 elimination and culminate in hypercapnia.[28,47-49]

Symptoms, Signs, and Physiologic Consequences of Hypercapnia

Life-threatening manifestations may occur with either severe acute respiratory acidosis or with acute decompensation in a patient with chronic hypercapnia. In either instance, it is crucial to remember that hypercapnia typically occurs in conjunction with hypoxemia. In fact, when a respiratory arrest takes place under room air conditions, life-threatening hypoxemia develops well in advance of important hypercapnia. Because of the large body stores of CO_2, P_{aCO_2} increases by only 3–5 mm Hg/min after the cessation of ventilation.[4] In contrast, clinically important severe hypercapnia may occur when supplemental oxygen blunts the decrease in P_{aO_2}. Importantly, CO_2 rapidly crosses cellular membranes, leading to a prompt reduction in intracellular pH.[50] The effect of intracellular buffers, decreased proton generation, and alterations in transmembrane ion exchange can result in the intracellular pH returning to near normal in several hours.[51] Therefore, acute hypercapnia has the potential to rapidly affect many organ systems.

Central Nervous System

The clinical manifestations of acute hypercapnia are predominantly neurologic. In the extreme this is often referred to as CO_2 narcosis or hypercapnic encephalopathy. The presence and nature of these symptoms depends on the magnitude of hypercapnia and acidemia, the rapidity of the change in P_{aCO_2} and pH, and the degree of concomitant hypoxemia. In acute hypercapnia, CO_2 rapidly diffuses across the blood-brain barrier to increase the cerebrospinal fluid $[H^+]$ and lower the cerebrospinal fluid pH. These effects are transient because, by approximately 24 hours, the cerebrospinal fluid $[HCO_3^-]$ increases to that seen in the plasma, and the cerebrospinal fluid pH increases. One consequence of the acute hypercapnic effect is vasodilation of the cerebral vasculature, an increase in cerebral blood flow and cerebral blood volume, an increase in intracranial pressure, and a decrease in cerebral compliance.[52–54] It appears that these effects are pH-mediated, because the increased intracranial pressure related to acute hypercapnia can be blocked by concomitant bicarbonate administration to keep the pH at 7.40.[55]

The principal neurologic manifestations of acute respiratory acidosis and hypercapnia are anxiety, irritability, inability to concentrate, confusion, disorientation, restlessness, somnolence, lethargy, and agitation.[4] Headache is often present at night and upon awakening in the morning. Psychosis may be present and manifest as euphoria, hallucination, delusions, or delirium.[4] Stupor and coma appear to be rare and are only seen when P_{aCO_2} is markedly elevated, typically exceeding 70–100 mm Hg. The physical examination may reveal tremor, slurred speech, myoclonus, asterixis, pupillary constriction, and blurring of the optic discs or papilledema.[4] Deep tendon reflexes are often brisk with mild to moderate hypercapnia but diminished when P_{aCO_2} elevation is severe.[4,16,17]

Cardiovascular

Acute mild to moderate hypercapnia produces increased release of circulating catecholamines (both epinephrine and norepinephrine) and direct peripheral vasodilation through inhibition of vascular smooth muscle.[50,56–58] Administration of bicarbonate to correct the pH can blunt the increase in catecholamines.[56] The results of these effects are a hyperdynamic state with increased cardiac output, decreased systemic vascular resistance, and increased heart rate with a normal or elevated blood pressure.[59–61] Correction of the acidemia with bicarbonate appears to attenuate the increased cardiac output.[55] Acute hypercapnia can produce a transient reduction in cardiac contractility by interfering with the effect of calcium on myofilaments.[62,63]

On exam, the skin is flushed and warm, the patient diaphoretic, and the arterial pulses bounding. In contrast, when hypercapnia is severe or associated with substantial hypoxemia, hypotension may be present because of direct myocardial depression.[64,65] The incidence of cardiac arrhythmias (usually supraventricular tachyarrhythmias) is increased, often because of hypoxemia, rapid fluctuations in electrolytes, and increased sympathetic tone, rather than hypercapnia-induced cardiac irritability. Hypercapnia also causes a rightward shift of the hemoglobin dissociation curve, favoring unloading of oxygen at the tissue level and therefore enhancing overall oxygen delivery and maintenance of oxygen consumption.[59,61,66,67] It must also be remembered that cardiogenic pulmonary edema itself can be the cause of hypercapnia.[68]

Pulmonary/Respiratory

In the absence of central or peripheral nervous system depression, acute hypercapnia is associated with severe dyspnea and distress. It appears that hypercapnia alone can cause an increase in inspiratory effort sensation independent of the simultaneous increase in $\dot{V}_E$ that may accompany it.[69] Hypercapnia leads to a decrease in P_{AO_2}, and,

therefore, P_{aO_2}, as predicted by the alveolar air equation. One consequence is the resulting hypoxic pulmonary vasoconstriction and acute pulmonary hypertension. The direct effect of acute hypercapnia in normals is controversial, though pulmonary artery pressures and pulmonary vascular resistance may increase.[70] Hypercapnia itself has a mild pulmonary vasoconstrictive effect, but this is probably mediated more by the hydrogen ion concentration than by the CO_2 tension.[71,72] Respiratory acidosis does substantially potentiate the vasoconstrictive effects of hypoxia. In patients with acute lung injury, acute hypercapnia (permissive hypercapnia) causes an increase in pulmonary artery pressures, though pulmonary vascular resistance may not increase.[59–61] One reason for the observed pulmonary hypertension may be the increased flow across the pulmonary circulation that results from an increase in cardiac output.

The effects of acute respiratory acidosis on respiratory muscle function are controversial. Juan et al,[73] in a small study of normal men, found that acute respiratory acidosis decreases diaphragmatic contractility and endurance time. In contrast, Mador et al[74] found no decrease in diaphragmatic contractility with acute hypercapnia. It has also been observed that hypercapnia did not reduce maximum ventilatory capacity and did not intensify long-lasting fatigue, but it did augment the reduction in diaphragmatic contractility after sustained maximal ventilation.[75]

Renal

Renal hemodynamics appear to be affected by changes in both oxygen and CO_2 levels. In hypoxemic COPD patients it has been demonstrated that renovascular resistance decreases when hyperoxemia is induced. In contrast, hypercapnia causes an increase in renovascular resistance and appears to override the vasodilating effects of hyperoxemia.[76] Hypercapnia has been associated with retention of both sodium and water, especially when there is concomitant right ventricular dysfunction. Suggested mechanisms include increased antidiuretic hormone release, increased cortisol secretion and direct stimulation of the renin-angiotensin system.[4]

Chronic Hypercapnia

Chronic hypercapnia is typically less dramatic in presentation because organ systems have a chance to compensate for both the increase in P_{aCO_2} and the decrease in pH. For example, patients with chronic hypercapnia may have no or minimal neurologic symptoms despite P_{aCO_2} greater than 100 mm Hg. One explanation is that, unlike in acute hypercapnia, cerebral blood flow appears to be normal in chronic hypercapnia.[77] The only clinical signs may be morning headaches, mild irritability, lethargy, and a disturbed sleep pattern with a reversal of sleep/wake cycle. Respiratory symptoms may be minimal because of desensitization of dyspnea and changes in the set point for the respiratory controller. Because of a sedentary lifestyle, respiratory failure is frequently insidious in patients with neuromuscular disease. Chronic increase in the respiratory load may also depress the ventilatory response to hypercapnia.[78–80]

Other Effects

Respiratory acidosis, as with metabolic acidosis, may affect gastric antral rhythms and fundic tone and therefore may contribute to gastroparesis.[81] With both acute and chronic hypercapnia it is common to see a mild increase in serum sodium levels. Hyperphosphatemia can occur with acute hypercapnia secondary to release of phosphate from tissue sources. Chronic respiratory acidosis augments urinary calcium excretion by inhibiting tubular absorption.[82] In contrast, unlike metabolic acidosis, chronic respiratory acidosis does not appear to cause a negative calcium balance.[83]

Assessment of Respiratory Acidosis and Hypercapnia

The most common method of assessing hypercapnia and respiratory acidosis is through sampling of arterial blood via either direct arterial puncture or an indwelling intra-arterial catheter. The sample should be collected anaerobically into a tube with anticoagulant (usually heparin) and processed immediately or cooled to 4° C if analysis must be delayed. With this technique, arterial pH and the P_{CO_2} are directly measured and then used to calculate the plasma bicarbonate. Plasma bicarbonate can be separately determined by sampling venous blood and measuring the plasma total CO_2 concentration (95% of which is plasma bicarbonate).[84] It is crucial to realize that measurement errors can occur with each of these techniques. Accurate determination of arterial blood depends on proper calibration of the pH and P_{CO_2} electrodes. Fortunately, as predicted by the mass action equation for the bicarbonate-carbonic acid system, $[H^+]$, $[HCO_3^-]$, and P_{CO_2} are always in equilibrium (as represented by the Henderson equation).[84] Arterial blood gas (ABG) analysis results should always be checked against the Henderson equation (using the measured HCO_3^-) to ensure the validity of the values. Another source of error can be mistaking venous blood for an arterial sample. It is important to remember that the P_{CO_2} is higher in a venous sample, by approximately 6 mm Hg, because peripheral tissues add CO_2 to the venous blood.[84] Excessive heparin can cause a dilutional effect that lowers the readings for both P_{CO_2} and HCO_3^-. This problem can be substantially overcome by using lyophilized heparin.[85] One major drawback of arterial blood sam-

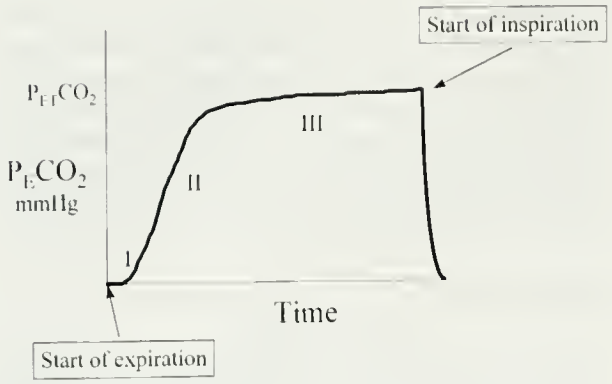

Fig. 5. Normal capnogram showing plot of expired carbon dioxide tension (P_{eCO_2}) versus time. Phase I represents expired gas from the anatomic dead space. Phase II represents a mixture of dead space and alveolar gas. Phase III represents alveolar gas. The end-tidal carbon dioxide (P_{etCO_2}) is the carbon dioxide tension at end-expiration (or start of inspiration).

pling is the invasive nature of the test. In addition, the intermittent nature of the data acquisition and the possible delay in obtaining results does not provide for "real-time" information.

Another analytic consideration is that during circulatory failure, ABG analysis may provide misleading information about the patient's acid-base status. Specifically, in the setting of adequate ventilation, severe circulatory failure or cardiac arrest are characterized by very large arteriovenous differences in pH and P_{aCO_2} (pH is 0.10–0.30 higher and P_{CO_2} is 20–45 mm Hg lower in arterial blood than in mixed venous blood). When concomitant severe respiratory failure is present, the arteriovenous differences are negligible, approaching those seen in the absence of circulatory shock.[47,48,85]

End-Tidal Carbon Dioxide Measurements

Arterial CO_2 can be estimated by measuring the CO_2 concentration in expired gas by a technique called capnography. During mechanical ventilation, infrared light absorption is the most common method of performing capnography on a breath-by-breath basis.[86] Two types of analyzers are in common clinical use. With a mainstream analyzer the sampling chamber is a part of the ventilator circuit. Delay time in analysis of gas is minimized with this circuit, but it is bulky and may be cumbersome to use. With a sidestream analyzer, a sample of gas is drawn off via small-bore tubing to a remote analyzer. Though less cumbersome, the tubing may become clogged with secretions. The output from these analyzers is typically displayed as a capnogram (Fig. 5), with special attention focused on the determination of the end-tidal CO_2 (P_{ETCO_2}). In a healthy subject with minimal dead-space ventilation, P_{ETCO_2} approximates P_{aCO_2}. In critically ill patients with lung pathology that increases the dead-space, P_{ETCO_2} does not accurately predict P_{aCO_2}. Elevated P_{ETCO_2} indicates hypercapnia but the magnitude cannot be known with certainty. More importantly, hypercapnia may be present in the setting of a normal or decreased P_{ETCO_2}. P_{ETCO_2} can be used to assess the adequacy of cardiopulmonary resuscitation, since a low P_{ETCO_2} indicates poor pulmonary perfusion as a result of inadequate resuscitation.[87] As a result, capnography has been used as a prognostic marker for the outcome of cardiopulmonary resuscitation.[88,89]

Common Clinical Conditions Associated with Hypercapnia and Respiratory Acidosis

Chronic Obstructive Pulmonary Disease

A substantial proportion of patients with severe COPD, usually chronic bronchitics or "blue bloaters," have longstanding hypercapnia. Although the incidence increases with worsening obstructive physiology (eg, forced expiratory volume in the first second < 1 L or $< 35\%$ of predicted), the correlation between P_{aCO_2} and indices of air flow obstruction is relatively poor. Hypercapnia has been thought to be a poor prognostic factor, though the issue is controversial.[90,91] Possible mechanisms for hypercapnia include a reduction in ventilatory drive, respiratory muscle dysfunction (mechanical disadvantage, weakness or fatigue), or increased wasted ventilation from $\dot{V}/\dot{Q}$ mismatch (increased dead space) in the setting of increased resistive and elastic work of breathing (WOB).

Approximately 15% of the population has a reduced ventilatory response to CO_2, with these individuals being more susceptible to CO_2 retention in the face of respiratory diseases. A genetic influence is possible, because blood relatives of patients with hypercapnic COPD may have an abnormal response to hypoxia and hypercapnia.[92] Additional causes of blunted CO_2 response in hypercapnic COPD include the effects of chronic hypoxia, the effects of chronic hypercapnia, and the buffering effects of chronic hyperbicarbonatemia.[3,4,87,93,94] In examining respiratory drive in COPD, investigators found increased but similar values for $P_{0.1}$ (mouth occlusion pressure in the first 0.1 second of inspiration) in patients with and without hypercapnia.[95] This observation suggests that respiratory drive is abnormal in hypercapnic COPD, because one would expect a higher $P_{0.1}$ in the setting of an elevated P_{aCO_2}.

Respiratory muscle dysfunction appears to be abnormal in COPD and this may contribute to hypoventilation and CO_2 retention. Hyperinflation and consequent diaphragmatic flattening decrease the capacity to generate inspiratory pressure by reducing the zone of apposition, altering the insertional forces between diaphragm and lower rib cage and increasing the radius of curvature of the mus-

cle.[43,96] Although acute reductions in diaphragmatic length (eg, acute hyperinflation) decrease maximum force generation, adaptation during chronic hyperinflation appears to maintain the muscles' force-length relationships.[97] Similarly, in the absence of malnutrition, steroid myopathy, or an acute myopathic process, intrinsic respiratory muscle dysfunction does not appear to be present. Acute respiratory muscle fatigue may be present when respiratory capacity is overwhelmed by an increase in WOB.[98] In contrast, to date there is no convincing evidence that a state of chronic respiratory muscle fatigue exists to explain hypercapnia.

Whatever the cause of the elevated P_{CO_2} in COPD, it is relevant that these muscles must confront both increased resistive and elastic (related to dynamic hyperinflation) loads. In a study of 311 stable COPD patients, Begin and Grassino[99] found that chronic alveolar hypoventilation was most likely to develop in patients who had a combination of elevated inspiratory load and inspiratory muscle weakness.

Patients with hypercapnic COPD may demonstrate severe $\dot{V}/Q$ mismatching, with an elevation of dead-space ventilation.[44,100] Another factor contributing to increased dead space is the rapid shallow breathing pattern seen in this setting.[95,101–103] Compared to eucapnic COPD patients, those with hypercapnia have lower V_T, similar or increased respiratory rate, and similar or decreased $\dot{V}_E$.[95,101–103] The pathogenesis of rapid shallow breathing remains uncertain, but may reflect stimulation of the irritant or J receptors, the imbalance between respiratory load and capacity, or abnormal neuromuscular coupling.

Obesity Hypoventilation Syndrome

Some morbidly obese patients (body mass index > 40 kg/m^2) may have a syndrome characterized by chronic hypoventilation and chronic respiratory failure (obesity hypoventilation syndrome). Studies of patients with obesity hypoventilation syndrome indicate that they have both reduced ventilatory drive and increased WOB.[32,104,105] Acute hypercapnia can also occur because of periodic breathing with an associated temporal $\dot{V}/Q$ mismatch.[106] The WOB increases because the total respiratory system compliance is reduced secondary to chest wall and abdominal influences and probably microatelectasis.[17,104,107] An element of respiratory muscle dysfunction may also be present, possibly because of fatty infiltration of the muscles.[108] The imbalance between respiratory muscle capacity and load may help explain why patients with obesity hypoventilation syndrome tend to have a more rapid and shallow breathing pattern than obese patients with eucapnia.[36] Patients with obesity hypoventilation syndrome are prone to develop obstructive apnea during sleep and this may contribute to further elevations of P_{aCO_2}.[36] Conversely, only a small fraction of patients with primary obstructive sleep apnea manifest daytime hypercapnia, and these patients appear to have concomitant airways disease.[109,110]

Respiratory Muscle Weakness

A wide array of neuromuscular diseases have been associated with respiratory muscle weakness.[43] Respiratory muscle involvement may be part of a more generalized neuromuscular process (eg, amyotrophic lateral sclerosis or muscular dystrophy) or may represent the disease's only manifestation. Patients with neuromuscular disease can present with hypercapnic respiratory failure, though many have a paucity of symptoms at presentation.[111–117] A pattern of rapid and shallow breathing is frequently observed, and this contributes to hypercapnia by increasing the fraction of total $\dot{V}_E$ that is wasted. Most patients with neuromuscular respiratory disease exhibit an increase in respiratory drive when assessed via either mouth occlusion pressure ($P_{0.1}$) or electromyogram of the diaphragm.[118] In contrast, some diseases of the neuromuscular system, such as myotonic dystrophy and hypothyroidism, also affect the respiratory controller and may be associated with decreased respiratory drive.[31,119]

Special Considerations

Worsening Hypercapnia in Response to Supplemental Oxygen Therapy

Supplemental oxygen therapy given to a patient with COPD exacerbation may lead to worsening hypercapnia.[120] It was traditionally thought that this was secondary to removal of hypoxic ventilatory drive, which superseded hypercapnic ventilatory drive when chronic hypercapnia was present. Aubier et al[121] compared 20 COPD patients in their chronic states and in ARF, and found that supplemental oxygen reduced the $\dot{V}_E$ by 14% because of a small decrease in respiratory rate. This was not thought to contribute entirely to the observed hypercapnia. A subsequent study of patients with COPD and ARF examined the effect of breathing 100% oxygen and found a transient decrease in $\dot{V}_E$.[122] Within 15 minutes $\dot{V}_E$ increased to 93% of the control value, but P_{aCO_2} remained elevated by an average of 23 mm Hg (and showed no correlation with $\dot{V}_E$). Based on their analysis, the authors attributed the hypercapnia to an increase in dead space ventilation and $\dot{V}/\dot{Q}$ mismatch due to the loss of hypoxic pulmonary vasoconstriction. This finding that the major component in hypercapnia is worsening $\dot{V}/\dot{Q}$ ratio and not a decrease in ventilatory drive was subsequently confirmed by Dick et al[123] and Sassoon et al.[124] An investigation of mechanically ventilated patients found that, following a period of normoxia, a further increase in F_{IO_2} did not result in greater hypercapnia.[125] However, a recent study divided patients with

acute exacerbation of COPD into CO_2 retainers and CO_2 nonretainers and examined their ventilatory drives and $\dot{V}/\dot{Q}$ matching using the multiple inert gas elimination technique.[126] The authors found equivalent reductions in $\dot{V}/\dot{Q}$ ratio and increased dead space in both groups, but a worsening of respiratory drive in the CO_2 retainers. It thus appears that the hypercapnia seen with supplemental O_2 therapy in COPD is multifactorial. Hypoxia at baseline and acidosis are better predictors of oxygen-induced CO_2 narcosis than hypercapnia.[126,127]

Another factor contributing to hypercapnia is the Haldane effect (the decreased hemoglobin affinity for CO_2 in the presence of increased oxygen saturation).[128,129] In essence this creates excess CO_2 that must be eliminated through an increase in $\dot{V}_A$. The magnitude of this effect is controversial and may account for 30–78% of the observed increase in P_{aCO_2}.[130,131] A computer simulation model found that oxygen-induced hypercapnia could be entirely accounted for by a combination of the Haldane effect and the release of hypoxic pulmonary vasoconstriction, leading to an increase in physiologic dead space.[132]

Lastly, hypercapnic COPD patients requiring long-term oxygen therapy are also at risk for worsening hypercapnia, especially during sleep. Studies have demonstrated that concomitant use on nocturnal noninvasive ventilation can counter alveolar hypoventilation and improve ABG values, sleep, and quality of life.[133]

Asthma

Hypercapnia is a sign of severe air flow obstruction in a patient with status asthmaticus. Recent investigations indicate that the majority of patients with asthma and hypercapnia do not require mechanical ventilation but improve with medical therapy within 16 hours.[134] Chien et al[135] examined in acutely ill asthmatics the effect of breathing 100% oxygen for 20 minutes. Hypercapnia developed in nearly 67%, with increases ranging from 1–10 mm Hg, and was most likely to occur in patients with the most severe airway obstruction. Although the increase in P_{aCO_2} was modest, the authors speculated that more prolonged hyperoxia may lead to severe hypercapnia.

Others

Oxygen therapy can worsen hypercapnia in patients with neuromuscular disease and diaphragmatic dysfunction and in some patients with obesity hypoventilation syndrome.[36,136]

Permissive Hypercapnia

Accumulating animal and human evidence indicates that application of low V_T (low stretch or lung-protective strategy) during mechanical ventilation of patients with acute lung injury may decrease ventilator-associated lung injury and improve outcomes.[137–140] Unless respiratory frequency is substantially increased, a reduction in V_T leads to decreased $\dot{V}_A$ and consequent hypercapnia, which may be severe (so-called permissive hypercapnia).[141] Concerns about severe elevations of P_{aCO_2} have led investigators to try alternative methods of CO_2 elimination, including extracorporeal techniques and tracheal gas insufflation.[142–144] Reports indicate that the manifestations of acute severe respiratory acidosis are generally well tolerated and reverse rapidly on reestablishment of adequate ventilation.[145–147] It also appears that hypercapnia is well tolerated when it develops as a result of a lung-protective ventilatory strategy.[141,148] Importantly, these studies have generally excluded patients with elevated intracranial pressure and those with severe concomitant metabolic acidosis. A strategy of "controlled hypoventilation" has been successfully applied to prevent barotrauma and cardiovascular collapse in patients with status asthmaticus.[149–151] Although in general this strategy appears to be safe, there are case reports of hypercapnia-associated CNS injury.[152–154]

Recently, investigators have suggested that hypercapnia may have an independent protective or therapeutic benefit.[155] In an animal model of acute lung injury, hypercapnic acidosis exerted a protective effect by inhibition of endogenous xanthine oxidase.[156] This protective effect appears to be related to extracellular acidosis rather than the elevation of CO_2.[157] In contrast, hypercapnic acidosis, but not metabolic acidosis, was highly protective in an ischemia-reperfusion myocardial injury model.[158] Similarly, in a swine model of coronary artery occlusion, acute hypercapnia led to an increase in global coronary blood flow.[159] It has also been recently found that a brief period of moderate hypercapnia was neuroprotective in an animal model of brain ischemia.[160]

Approach to the Patient with Respiratory Acidosis

Assessment always begins with a thorough history and physical examination aimed at identifying the elements seen with the disorders listed in Tables 1 and 2. Specifically, the clinician should seek evidence of dyspnea (at rest or with exertion), wheezing, cough, sputum production, and evidence of exercise limitation. Symptoms suggestive of respiratory muscle weakness (difficulty rising from chair, difficulty combing hair, orthopnea) and of sleep disordered breathing (snoring, morning headaches, daytime hypersomnolence) should be sought. Because of a sedentary lifestyle, patients with neuromuscular disease may have minimal or no respiratory symptoms. On physical examination, the clinician should focus on the respiratory rate, the use of accessory respiratory muscles, the presence of Hoover's sign and thoracoabdominal paradox,

the quality of breath sounds, the degree of tidal excursion, the presence of adventitious sounds, and clubbing. The finding of inspiratory stridor is important because it indicates that upper airway obstruction is present.[161,162] Evidence of right-sided heart failure should be sought, including jugular venous distention, a right-sided S_3, hepatomegaly, and lower extremity edema. A chest radiograph is a crucial component of the evaluation, because the presence of clear lung fields narrows the diagnostic considerations to neuromuscular disease, airways or pulmonary vascular disease, or decreased central respiratory drive. The presence of hyperbicarbonatemia and erythrocytosis suggest that hypercapnia may be chronic rather than acute. Unfortunately, the clinical examination is insufficiently sensitive to reliably estimate either the total $\dot{V}_E$ or the V_A. Therefore, the clinical examination must always be supplemented by direct measurement of the pH and P_{aCO_2} via ABG analysis. It must be emphasized that although pulse oximetry gives insight into the adequacy of oxygenation, it provides no information on the adequacy of ventilation or the acid-base status.[163]

The coexistence of acidemia (reduced pH) and hypercapnia is diagnostic of respiratory acidosis. If alkalemia is present, the clinician should consider metabolic alkalosis as the cause of hypercapnia (eg, secondary hypercapnia). One of the initial steps in assessing the hypercapnic patient is determining if the process is acute or chronic (Table 5). With acute hypercapnia, one should expect a 1 mEq/L increase in HCO_3^- and 0.08 unit decrease from a normal pH of 7.40 for every 10 mm Hg increase in P_{aCO_2}. With chronic hypercapnia one should expect a 3.5 mEq/L increase in HCO_3^- and 0.03 unit decrease from a normal pH of 7.40 for every 10 mm Hg increase in P_{aCO_2}. Changes that fall between these two extremes suggest the presence of both acute and chronic respiratory acidosis. When a metabolic acidosis is superimposed, both the pH and the plasma bicarbonate will be lower than expected. Conversely, when metabolic alkalosis is present, both pH and plasma bicarbonate will be higher than expected. Analysis of P_{aO_2} and calculation of the $P(A\text{-}a)O_2$ is also of diagnostic importance. The combination of hypoxemia, hypercapnia, and a normal $P(A\text{-}a)O_2$ is diagnostic of hypoventilation (eg, respiratory muscle weakness, central respiratory depression). Conversely, the presence of a widened $P(A\text{-}a)O_2$ indicates the presence of V/Q mismatching, as would be seen with airway or parenchymal disorders.

Table 5. Equations for Determining Whether Respiratory Acidosis Is Acute or Chronic

Acute respiratory acidosis: $\Delta pH_a = \Delta P_{aCO_2} \times 0.008$
For example: If P_{aCO_2} rises from 40 mm Hg (normal) to 60 mm Hg $\Delta pH_a = (60\text{–}40) \times 0.008 = 0.16$, pH_a will decrease from 7.40 to 7.24
Chronic respiratory acidosis: $\Delta pH_a = \Delta P_{aCO_2} \times 0.003$
For example: If P_{aCO_2} rises from 40 mm Hg to 60 mm Hg $\Delta pH_a = (60\text{–}40) \times 0.003 = 0.06$, pH_a will decrease from 7.40 to 7.34

ΔP_{aCO_2} = change in arterial oxygen tension
ΔpH_a = change in arterial pH

Medical Therapy

Treatment for respiratory acidosis depends in part on whether the process is acute or chronic and can be divided into therapies directed at the specific disease process and therapies directed at abnormalities in gas exchange. Disease-specific interventions include treating drug overdose causing respiratory depression and hypoventilation with specific antidotes such as flumazenil for benzodiazepines and naloxone for narcotics. Inhaled bronchodilators, steroids, theophylline, and antibiotics are used to treat exacerbations of COPD. Medications that may depress respiratory drive (sedatives) must be avoided. Similarly, it is crucial to avoid electrolyte abnormalities that can adversely affect respiratory muscle function, such as hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia. Patients with hypercapnic COPD often have concomitant heart failure as a precipitating cause of ARF. When diuretics are used, adequate chloride must be supplied to avoid the development of a metabolic alkalosis that could blunt respiratory drive.[164] Nutritional therapy must be carefully assessed to avoid overfeeding, as this may contribute to increase of $\dot{V}_{CO_2}$.

Hypoxemia inevitably accompanies acute respiratory acidosis, so supplemental oxygen is applied to achieve an oxygen saturation of 90% or a P_{aO_2} of 60 mm Hg. Avoiding excess oxygen administration can be achieved by using very low flow settings (< 2 L/min) with a nasal cannula or by employing an air-entrainment mask.[165] If severe hypercapnia develops, abrupt withdrawal of oxygen therapy should be avoided because of the risk of profound hypoxemia. If higher flow oxygen is needed, combination with noninvasive mechanical ventilation may be effective.

Alkali Therapy

Alkali therapy (eg, sodium bicarbonate) should not be used to treat the acidosis that results from primary hypercapnia. Such therapy has considerable risks, including an immediate increase in CO_2 production, worsening cellular acidosis, and a pH-mediated depression of respiratory drive. When metabolic acidosis complicates respiratory acidosis, alkali therapy may be cautiously considered.[4] This might be particularly the case where the metabolic acidosis is causing extreme tachypnea. On theoretical grounds, alkali therapy might improve the responsiveness of bronchial

smooth muscle to beta adrenergic agents when bronchospasm coexists with acidemia.[16]

Some investigators have advocated the use of the strong organic base tris(hydroxymethyl)aminomethane (THAM) based on its capacity to promote CO_2 removal as HCO_3^- is generated (Equation 7).

$$THAM + CO_2 + H_2O \leftrightarrow THAM^+ + HCO_3 \quad (7)$$

In reality, the amount of CO_2 removed is trivial, and therefore this agent appears to be of marginal clinical benefit.

Ventilatory Support

When respiratory acidosis incompletely responds to medical interventions or is severe, mechanical ventilatory support is indicated. Effective ventilatory support can reduce P_{aCO_2} and reverse respiratory acidosis by decreasing WOB (decreased $\dot{V}_{CO_2}$), increasing total $\dot{V}_E$, and reducing dead space ventilation by improving the breathing pattern.[166] There is now strong evidence that noninvasive ventilation delivered through a nasal or full face mask improves the outcome of ARF, especially in COPD.[167,168] Although randomized controlled trials are not yet available, observational studies suggest that noninvasive ventilation is also effective for acute asthma and ARF related to obesity hypoventilation syndrome.[169] In the presence of apnea, immediate tracheal intubation and mechanical ventilation are indicated. In the setting of an unstable patient or when noninvasive ventilation fails, intubation should be carried out to allow for invasive ventilatory support. There are no absolute ABG analysis criteria to determine when intubation is required. In general, it should be considered when pH is less than 7.10–7.25 or P_{aCO_2} is greater than 80–90 mm Hg. For patients with hypovolemic or septic shock, volume resuscitation is crucial because adequate pulmonary perfusion is necessary to effectively eliminate CO_2.

Though invasive mechanical ventilation is often necessary in patients with hypercapnic COPD and ARF, clinicians may become concerned about the chances for successful extubation. Recent data indicate that these patients have a high likelihood of being successfully liberated from mechanical ventilation.[170] Nevertheless, there are important risks to invasive mechanical ventilation in patients with chronic hypercapnia. First, a high $\dot{V}_E$ will predispose to dynamic hyperinflation and intrinsic positive end-expiratory pressure, with the risk of cardiovascular compromise, barotrauma, and worsening gas exchange. Excessive $\dot{V}_E$ may too rapidly lower P_{aCO_2}, resulting in clinically important alkalemia before the kidney has the opportunity to excrete excess bicarbonate. For example, abruptly normalizing P_{aCO_2} from 80 mm Hg to 40 mm Hg in a patient with chronic hypercapnia would immediately increase the pH from 7.28 to 7.54. This rapid lowering of P_{aCO_2} and increased pH has the potential to decrease cerebral blood flow, decrease cardiac output, or precipitate seizures or cardiac arrhythmias.[171] In fact, the best approach in a patient with chronic hypercapnia is to apply a $\dot{V}_E$ that targets the patient's long-term baseline P_{aCO_2}. Maintaining P_{aCO_2} well below the long-term baseline for several days will result in renal bicarbonate excretion and this may interfere with weaning from mechanical ventilation. As the patient's respiratory system tries to return to baseline P_{aCO_2} during spontaneous breathing trials, a precipitous decrease in pH may occur as bicarbonate buffering is diminished. This acidemia increases respiratory drive and may force the patient with limited respiratory reserve to increase $\dot{V}_E$, at the risk of respiratory muscle fatigue. When post-hypercapnic metabolic alkalosis is present, adequate chloride must be provided to allow for excess bicarbonate to be excreted by the kidney. If post-hypercapnic metabolic alkalosis is slow to resolve, acetazolamide may be used.

Outpatient Evaluation

For patients with chronic respiratory acidosis, pulmonary function testing should be carried out, including spirometry, flow-volume loop, lung volumes, and diffusion capacity, looking for either obstructive or restrictive lung disease. A reduced maximum voluntary ventilation suggests either upper airway obstruction or neuromuscular weakness. Reduced maximum inspiratory and expiratory pressures can help confirm a diagnosis of respiratory muscle weakness.[36] A reduction in vital capacity by 30–40% in the supine position (compared to upright) suggests diaphragmatic dysfunction.[172] When sleep-disordered breathing is suspected, a polysomnogram should be performed. Although assessing ventilatory control with a CO_2 rebreathing test has been advocated, abnormal responses can be seen with depressed respiratory drive, neuromuscular disease, or severe air flow obstruction. In each instance the patient may be unable to augment ventilation by the expected 1–7 L/min for each 1 mm Hg increase in P_{aCO_2}.[173]

For chronic, stable patients, long-term nocturnal noninvasive ventilation appears to be beneficial for inpatients with obesity hypoventilation syndrome or neuromuscular or chest wall diseases, but efficacy in COPD patients remains controversial.[174,175] Respiratory stimulants such as progesterone have been effective in patients with obesity hypoventilation syndrome.[176]

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Respiratory Alkalosis

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Respiratory alkalosis is an extremely common and complicated problem affecting virtually every organ system in the body. This article reviews the various facets of this interesting problem. Respiratory alkalosis produces multiple metabolic abnormalities, from changes in potassium, phosphate, and calcium, to the development of a mild lactic acidosis. Renal handling of the above ions is also affected. The etiologies may be related to pulmonary or extrapulmonary disorders. Hyperventilation syndrome is a common etiology of respiratory alkalosis in the emergency department setting and is a diagnosis by exclusion. There are many cardiac effects of respiratory alkalosis, such as tachycardia, ventricular and atrial arrhythmias, and ischemic and nonischemic chest pain. In the lungs, vasodilation occurs, and in the gastrointestinal system there are changes in perfusion, motility, and electrolyte handling. Therapeutically, respiratory alkalosis is used for treatment of elevated intracranial pressure. Correction of a respiratory alkalosis is best performed by correcting the underlying etiology. *Key words: respiratory alkalosis, acid-base, lactic acidosis, bicarbonate, hypocapnia, hyperventilation.* [Respir Care 2001;46(4): 384–391]

Introduction

Respiratory alkalosis is a common and important manifestation of acid-base disorder.[1] This respiratory acid-base disturbance may result from an alteration in carbon dioxide tension or may reflect a mixture of respiratory and superimposed metabolic components. Regardless of the type of disturbance, respiratory alkalosis affects every organ system in the body. This article reviews the definition,

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classification, and physiologic consequences of respiratory alkalosis. We will also discuss its symptoms, common causes, therapeutic uses, and treatment.

Definition

Respiratory alkalosis is a systemic acid-base disorder characterized by a primary reduction of arterial partial pressure of carbon dioxide (P_{aCO_2}), which produces an elevation in pH and a consequent decrease in bicarbonate (HCO_3^-) concentration.[2] In simple primary respiratory alkalosis, the respiratory disorder is the sole abnormality, in which the decrease in P_{aCO_2} results from an excess of alveolar CO_2 excretion over production. The respiratory system is normally kept in check by a negative feedback loop in which excess CO_2 excretion (alveolar hyperventilation) is limited by the inhibitory action of the resulting hypocapnia on the respiratory center. Respiratory alkalosis, however, can also occur as compensation for another underlying process such as metabolic acidosis or as a separate component of mixed acid-base disorders, in which case the levels of P_{aCO_2}, HCO_3^-, and pH are determined by the combined effects of the underlying acid-base disorders.

Classification

Respiratory alkalosis can be classified as acute or chronic. In acute respiratory alkalosis the decrease in P_{aCO_2} is accompanied by a mild but rapid decrease in serum HCO_3^- concentration, which occurs within minutes of the onset of hypocapnia, reaches a steady state level within 10 minutes, and remains so for up to 6 hours.[2] In chronic respiratory alkalosis, persistent hypocapnia triggers renal compensatory mechanisms, leading to a further decrease in serum HCO_3^- concentration and an increase of pH toward normal values. These adjustments begin about 6 hours after the onset of hypocapnia and become complete within 2–4 days. Except with patients on mechanical ventilation, in the clinical setting it is often difficult to discern the precise duration and stage of progression of respiratory alkalosis from acute to chronic.

Physiologic Response to Respiratory Alkalosis

Acute and Chronic Compensatory Mechanisms

To facilitate the discussion and understanding of the systemic response to this acid-base disorder, the modified Henderson-Hasselbalch equation, which relates hydrogen ion concentration to P_{aCO_2} and HCO_3^-, is shown below:

$$[H^+] = 24 \times \frac{P_{aCO_2}}{HCO_3^-} \quad (1)$$

This equation shows how a reduction in P_{aCO_2} leads to a decrease in the P_{aCO_2}/HCO_3^- ratio and a decrease in H^+ concentration, which then results in an increase in pH or alkalemia. The alkalemia in turn triggers the release of H^+ from intracellular and extracellular buffers, titrating HCO_3^-, and thereby lessening the increase in pH. However, the magnitude of this immediate response to acute respiratory alkalosis is quite small and is insufficient for substantially preventing the decrease of P_{aCO_2}/HCO_3^- ratio and the concomitant increase of pH. Consequently, in acute respiratory alkalosis, H^+ concentration decreases by about 0.8 nmol/L from 40 nmol/L for every 1 mm Hg decrease in P_{aCO_2} from 40 mm Hg.[3] In this instance, the relationship between changes of serum HCO_3^- and the decrease of P_{aCO_2} in Equation 1 can be written as follows:

$$\Delta HCO_3^- \text{ (nmol/L)} = 0.1 \times \Delta P_{aCO_2} \text{ (mm Hg)} \quad (2)$$

Thus, an acute P_{aCO_2} decrease from 40 to 20 mm Hg should lead to a rapid decline in serum HCO_3^-, of approximately 2 nmol/L (0.1 × 20), from the normal value of 24 nmol/L down to 22 nmol/L. Consequently, notable deviations of HCO_3^- concentration from the predicted value derived from Equation 2 indicate something other than isolated acute respiratory alkalosis.

In chronic respiratory alkalosis, renal compensatory mechanisms help to further reduce plasma HCO_3^- concentration via suppression of tubular H^+ secretion and HCO_3^- reabsorption. Consequently, the magnitude of the decrease in H^+ concentration in chronic respiratory alkalosis is greatly mitigated. In dogs in which hypocapnia was induced by exposure to 9% O_2, P_{aCO_2} decreased from 36 to 21 mm Hg while H^+ concentration decreased from 42 to 39.5 nmol/L.[4] Hence, there was a 0.2 nmol/L decrease in H^+ from 40 nmol/L for each 1 mm Hg decrease in P_{aCO_2} from 40 mm Hg. In a more recent study, induced chronic respiratory alkalosis in healthy humans exposed to high-altitude hypoxia for several days led to a decrease in H^+ concentration by 0.4 nmol/L from 40 nmol/L for each mm Hg decrease in P_{aCO_2} from 40 mm Hg.[5] Thus, the relationship between changes in serum HCO_3^- and P_{aCO_2} in chronic respiratory alkalosis can be written as follows:

$$\Delta HCO_3^- \text{ (nmol/L)} = 0.4 \times \Delta P_{aCO_2} \text{ (mm Hg)} \quad (3)$$

From Equation 3 one can calculate that a persistent decrease in P_{aCO_2} by 20 mm Hg will cause serum HCO_3^-

to decrease from 24 to 16 (24 − (0.4 × 20)) mmol/L. It should be noted that serum HCO_3^- rarely decreases below 12–14 mmol/L in patients with isolated chronic respiratory alkalosis, and its occurrence strongly indicates an independent component of metabolic acidosis.[1] Occasionally, however, serum HCO_3^- concentrations as low as 10 mmol/L have been observed.

Altered Electrolytes Homeostasis

In addition to triggering renal compensatory mechanisms, respiratory alkalosis leads to alterations in electrolyte homeostasis[6,9] and a modest increase in lactic acid production.[10,11] Hypokalemia or hyperkalemia,[6] hypophosphatemia[7,8] or hyperphosphatemia,[9] and decreased ionized calcium[9] have been shown to accompany respiratory alkalosis.

Acute respiratory alkalosis induced by hyperventilation results in initial hyperkalemia, followed by a rapid decrease in plasma potassium.[12] The hyperkalemia is due to hyperventilation-induced enhancement of alpha adrenergic activity. The hypokalemia is due to both transcellular shift and bicarbonaturia, which produce a direct increase in potassium excretion, providing cations to the bicarbonate anions. At the same time, potassium reabsorption by the collecting duct decreases so that potassium ions move into the cells in exchange for H^+ moving out of the cells. There is a linear relationship between the decrease in serum potassium and the increase in pH.[6] Serum potassium decreases 0.3 mmol/L for each 0.1 unit increase in pH.[6]

Serum and urine phosphate levels are also affected in respiratory alkalosis. Acutely, hypophosphatemia occurs as a result of increased intracellular uptake.[7] Conversely, chronic respiratory alkalosis causes hyperphosphatemia. The increase in serum phosphate is related to decreased urinary excretion of phosphate secondary to parathyroid hormone resistance.[8,9] The hyperphosphatemia can occur in conjunction with hypocalcemia.[9] This interesting effect of hyperphosphatemia appears to be secondary to the hypocapnia rather than the elevated pH or alkalosis,[8] and is modulated by beta receptors.[13–15] Dopamine enhances[13] whereas propranolol[15] blocks the phosphaturic effect of parathyroid hormone during acute respiratory alkalosis.

Lactic Acidosis

Another notable effect of respiratory alkalosis is the generation of lactic acidosis. As shown below, lactate is in equilibrium with pyruvate secondary to a reaction catalyzed by lactic dehydrogenase (LDH).

$$\text{Pyruvate} + \text{NADH} + H^+ = \text{lactate} + NAD^+ \quad (4)$$

Although lactate production is influenced by the relative levels of NADH (reduced nicotinamide adenine dinucleotide) versus NAD^+ (oxidized nicotinamide adenine dinucleotide), it also depends on the relative concentration of pyruvate. An increase in pyruvate can occur from a pH-induced increase in phosphofructokinase activity, producing rapid glycolysis.[16] In humans, acute hyperventilation with a decrease of P_{aCO_2} to 20 mm Hg and a corresponding pH of 7.61 results in a small increase in lactate, of less than 1 mmol/L.[10] Respiratory alkalosis not only increases the concentration, but also decreases the clearance of lactate, thereby increasing lactate levels even more.[11]

Etiology

The etiologies of respiratory alkalosis are multiple (Table 1) and include:

1. Hypoxia
2. Parenchymal lung disease
3. Bronchial asthma
4. Drugs and mechanical ventilation
5. Central nervous system disorders
6. Metabolic causes
7. Hyperventilation syndrome

Hypoxia

Hypoxemia and tissue hypoxia stimulate the chemoreceptors of the carotid bodies directly and indirectly, respectively, causing hyperventilation. The carotid bodies are comprised of glomus cells and sheath cells. The glomus cells release catecholamines when exposed to hypoxemia, stimulating the endings of the carotid sinus nerve fibers in the glossopharyngeal nerve. Interestingly, the glomus cells respond virtually solely to changes in arterial partial pressure of oxygen and not to changes in overall oxygen content, which explains why anemia and carbon monoxide poisoning do not cause considerable dyspnea or tachypnea.[17] Hypoxemia commonly occurs with a wide variety of pulmonary disorders, cyanotic heart disease, or exposure to high altitude.

The carotid bodies also respond to increasing H^+ concentration and thus respond indirectly to tissue hypoxia. Tissue hypoxia occurs with severe hypoxemia; cardiogenic, hypovolemic or septic shock; severe anemia; and hemoglobinopathies with high hemoglobin-oxygen affinity. Irrespective of the cause, tissue hypoxia increases production of lactic acid, which stimulates carotid body receptors, causing hyperventilation.

Parenchymal Lung Disease

Although parenchymal lung disease produces tachypnea via hypoxia, correction of hypoxemia does not always

Table 1 Causes of Respiratory Alkalosis

- Hypoxia
- Parenchymal lung disease
  - Pneumonia
  - Bronchial asthma
  - Diffuse interstitial fibrosis
  - Pulmonary embolism
  - Pulmonary edema
- Medications and mechanical ventilation
  - Medications
    - Salicylate
    - Nicotine
    - Xanthine
    - Catecholamines
    - Analeptics
  - Mechanical ventilation
- Central nervous system disorders
  - Meningitis, encephalitis
  - Cerebrovascular disease
  - Head trauma
  - Space-occupying lesion
  - Anxiety
- Metabolic
  - Sepsis
  - Hormonal
  - Pyrexia
  - Hepatic disease
- Hyperventilation syndrome

alleviate the dyspnea, which suggests that other mechanisms are at work. In rats, both inhibitory and excitatory vagal afferents in the lungs have been activated in various proportions in response to noxious stimuli such as acrolein[18] and wood smoke.[19] Histamine has similarly been shown to produce tachypnea and rapid shallow breathing in dogs.[20] In all of these trials, vagal blockade by cooling of the cervical vagus nerves abolished the responses.

Activation of vagal afferents most likely occurs also in asthma and pneumonitis. A recent trial in humans suggests that irritant receptors cause tachypnea in asthma.[21] The study measured respiratory frequency, tidal volume, and mean inspiratory flow in asthmatics and normals given inhaled methacholine. Asthmatics had a greater and more rapid respiratory frequency response at every degree of bronchoconstriction. It has also been shown that hydrogen peroxide stimulates pulmonary vagal afferents, which suggests that oxidative damage incites tachypnea in diseases such as acute respiratory distress syndrome and pneumonia.[22] In interstitial lung diseases such as idiopathic pulmonary fibrosis, tachypnea is thought to result from increased elastic load and stimulation of both mechanoreceptors of the chest wall and intrapulmonary receptors.[23]

Drugs and Mechanical Ventilation

Medications and mechanical ventilation are two commonly encountered reasons for respiratory alkalosis. Hyperventilation is a well-known clue to salicylate overdose, which produces hyperventilation by direct stimulation of central respiratory centers and by production of metabolic acidosis. Nicotine, xanthine derivatives (eg, theophylline), catecholamines, analeptics (eg, doxapram, nikethamide), and progestational hormones all increase minute ventilation. Medroxyprogesterone is used in patients with central hypoventilation. Doxapram is used in the intensive care unit setting to avoid intubation,[24] but is limited by its propensity to induce arrhythmia. In experimental animals, norepinephrine has been shown to stimulate the carotid peripheral chemoreceptors in a dose-dependent fashion, causing hyperventilation. Its effect is accentuated by the presence of hypoxemia.[25]

Hyperventilation is encountered in patients receiving mechanical ventilation.[26] The tendency for hyperventilation with assist-control modes of ventilation leads to the development of synchronized intermittent mandatory ventilation. However, changing to synchronized intermittent mandatory ventilation does not reliably remedy this problem.[27,28] Hence, use of sedatives with respiratory depressant effects or paralysis may be required. On the other hand, the current recommended protective ventilatory strategy in patients with acute respiratory distress syndrome (using small tidal volume)[29] may in fact cause hypercapnia.

Central Nervous System Disorders

Diffuse or focal involvement of the central nervous system can produce tachypnea. Diffuse processes such as meningitis or encephalitis can induce hyperventilation and respiratory alkalosis. In a study of patients with acute brainstem infarction, Lee et al[30] found that abnormalities in breathing pattern in the form of Cheyne-Stokes respiration or tachypnea were present with various degrees of respiratory alkalosis. Similarly, hyperventilation induced by a mass process such as brainstem astrocytoma has been described.[31]

Metabolic Disturbances

A variety of systemic disorders can produce respiratory alkalosis. Perhaps the most ominous is sepsis. Hyperventilation in sepsis is produced by both metabolic acidosis and direct lung injury, the latter mediated by vagal C-fiber afferents.[32] Interestingly, this same study suggested that there may be inhibitory responses mediated by the peripheral chemoreceptors attenuating the tachypnea.[32]

Progestins stimulate the respiratory center directly,[33] increase central chemoreceptor sensitivity to carbon diox-

ide,[34] and increase carotid body sensitivity to hypoxia,[33] thereby causing respiratory alkalosis. In the first two trimesters of pregnancy, 60–70% of women experience dyspnea, which is at least partially mediated by progestins.[35] A relative decrease in P_{aCO_2} in the latter part of the menstrual cycle has also been described.[36] Likewise, women on hormone replacement therapy develop respiratory alkalosis when placed on progestins.[37]

Pyrexia can also cause respiratory alkalosis. In a study by Fadic et al,[38] anesthetized cats warmed from a temperature of 37–40° C developed an increase in respiratory rate, tidal volume, and inspiratory flow. This effect was ablated with bilateral carotid neurotomy, suggesting that carotid body afferents contribute to the hyperventilation evoked by hyperthermia.

A well known cause of tachypnea is hepatic disease such as liver cirrhosis with portal-pulmonary hypertension,[39] hepatopulmonary syndrome,[40] and fulminant hepatic failure.[41] Although these situations are known to produce hypoxemia, tachypnea persists when the hypoxemia is corrected. The exact cause of the tachypnea remains unclear, but it is thought to be due to increased levels of progesterone, ammonia, and various amines.

Hyperventilation Syndrome

Hyperventilation syndrome, first described as "sighing dyspnea" by White and Hahn in 1929,[42] remains both a diagnosis of exclusion and questionable as a true clinical entity. The symptoms of this syndrome, shown in Table 2, are taken from a recent study of 23 patients experiencing acute hyperventilation in an emergency department,[43] and another study of 78 patients referred to a neurology clinic for unexplained neurological symptoms.[44] Virtually all of these symptoms can be explained by hyperventilation. Hyperventilation syndrome is reported to affect approximately 6–11% of the patient population, predominates in females, and seems to occur in the third to fourth decade of life.[45]

Table 2. Presenting Symptoms of Hyperventilation Syndrome

	Saisch et al (1996)[43] (%)	Perkin and Joseph (1986)[44] (%)
Dyspnea	61	53
Palpitations	13	32
Anxiety/Panic	30	NR
Paresthesia	35	36
Chest tightness/discomfort	30	8
Faintness/dizziness	13	59
Loss of consciousness	NR	13
Muscle spasm	9	NR

NR = not reported

The etiology of hyperventilation syndrome remains unknown, but it is strongly associated with psychiatric disorders, especially anxiety and panic. Currently the diagnosis of hyperventilation syndrome relies on the hyperventilation provocation test, during which the patients are voluntarily hyperventilated for a defined time period, most commonly 3 minutes (although some researchers continue for 30 min).[46] If the patient experiences symptoms similar to those during attacks, the test is considered positive.[47] The test is based on the assumption that hypocapnia is the primary trigger for the symptoms during the hyperventilation provocation test. Unfortunately, it has been found that patients suspected of hyperventilation syndrome, when challenged with isocapnic hyperventilation, experienced 66% of the symptoms listed on the questionnaire.[47] Hence, the relatively high false positive rate when isocapnic hyperventilation is performed calls the validity of the test into question.[47]

Clinical and Physiological Manifestations

Respiratory alkalosis can affect virtually every organ system in the body and produce a wide variety of clinical manifestations. These range from mild symptoms to fatal disease secondary to direct effects or secondary electrolyte abnormalities.

Central Nervous System

Central nervous system effects of hypocapnia are both central and peripheral. The threshold for these effects seems to be at P_{aCO_2} of $\leq$ 20 mm Hg, irrespective of the rate of P_{aCO_2} decrease.[48] The central symptoms are variable and range from vertigo, dizziness, anxiety, euphoria, clumsiness, and forgetfulness to hallucinations and absence seizure.[44] Unilateral somatic symptoms have also been reported. These symptoms are secondary to cerebral hypoxia arising from a reduction in cerebral blood flow brought about by changes in pH, rather than changes in P_{aCO_2}.[44,49]

The peripheral effects are related to increased neural excitability. Progressive hyperventilation has been shown to cause hypocalcemia, tetany, and increased afferent nerve activity corresponding to the development of paresthesias.[50,51] It is also postulated that the increased reactivity could be produced by decreases in phosphate levels rather than just decreases in calcium.[49]

Cardiovascular

Perhaps the most feared consequences of alkalosis and hypocapnia are cardiac disorders.[52] Tachycardia often occurs secondary to hypokalemia, triggered by increased sympathetic activity. The response of the heart to sympathetic stimulation itself also increases during acute alkalosis.[53]

Both ventricular[54] and atrial[55] arrhythmia may occur, which can at times be particularly refractory to pharmacologic intervention.

Chest pain secondary to cardiac and noncardiac causes is a common manifestation of hypocapnia. Respiratory alkalosis can produce cardiac ischemia in patients with or without coronary artery disease related to coronary vasoconstriction and increased oxygen affinity of hemoglobin at decreased pH.[56] Further, decreases in coronary blood flow have been shown to occur with decreased P_{aCO_2}.[57] Lastly, coronary vasospasm and atypical chest pain (Prinzmetal's angina) can also be precipitated by hyperventilation and prevented by pretreatment with calcium channel blockers.[58] Noncardiac chest pain is produced by esophageal spasm induced by hypocapnia. In most cases, however, the etiology is unclear but noncardiac in nature.

Pulmonary

It is well known that acute respiratory alkalosis can cause pulmonary artery vasodilation, with a resulting decrease in pulmonary vascular resistance. For this reason, it remains invaluable in the treatment of newborns with persistent pulmonary hypertension. Although the pulmonary artery vasodilation was initially thought to be specific for hypocapnia, studies show that in fact it is most closely related to changes in pH.[59,60] Respiratory alkalosis has also been shown to clearly attenuate thromboxane-induced pulmonary hypertension,[61] which is thought to be the underlying cause of pulmonary hypertension in infants with Group B beta-hemolytic *Streptococcus* and *Escherichia coli* pneumonia. In contrast, cyclooxygenase inhibition blocks respiratory alkalosis-induced vasodilation.[62] Although respiratory alkalosis causes acute pulmonary vasodilation, the effect on hypoxia-induced pulmonary vasoconstriction is not sustainable and, paradoxically, may worsen vasoreactivity to pressors and prostacyclin.[62,63] Hence, sustained respiratory alkalosis may be of limited efficacy in treating hypoxia-induced pulmonary hypertension.

In isolated perfused lungs, hypocapnia has been shown to both induce lung injury and potentiate acute lung injury following ischemic-reperfusion.[64] The range of pH studied was 7.60 to 8.30. The mechanisms of the lung injury may be related to increased microvascular permeability and result from increased production of dysfunctional surfactant.[65] Similar effects may have occurred in humans at extreme altitudes or during mechanical ventilation-induced respiratory alkalosis.

Gastrointestinal

Chronic respiratory alkalosis has no clinical effects on the gastrointestinal system, but acute respiratory alkalosis produces nausea, vomiting, and changes in gastrointestinal motility, as described in irritable bowel syndrome.[66] Most of these symptoms are produced via changes in central autonomic control, namely a decrease in central sympathetic outflow. This effect is critically dependent on the presence of hypocapnia, since only hypocapnic (and not eucapnic) hyperventilation produces increased colonic tone and phasic activity.[67] In anesthetized, mechanically ventilated dogs, hypocapnic hyperventilation not only affects gastrointestinal motility but also decreases splanchnic perfusion. Splanchnic perfusion was assessed by the gradient between gastric intramucosal CO_2 pressure and P_{aCO_2}.[68] However, in a similar study of critically ill patients who were hemodynamically stable, splanchnic perfusion did not change with acute hypocapnia.[69] Acute respiratory alkalosis also decreases ileal and colonic sodium and chloride absorption, as well as bicarbonate secretions.[70,71]

Diagnosis

When arterial pH is increased and P_{aCO_2} is decreased, a component of respiratory alkalosis exists. As described earlier, serum bicarbonate is only mildly reduced in acute respiratory alkalosis. The appropriateness of compensatory response can be assessed by using Equations 2 and 3 for acute and chronic respiratory alkalosis, respectively. If hypocapnia occurs with acidemia, a primary respiratory alkalosis exists if the degree of hypocapnia is greater than would be expected in response to the coexisting metabolic acidosis.

Therapeutic Uses

Induction of a respiratory alkalosis for patients with elevated intracranial pressure (ICP) is commonly performed. However, the overall benefit in comparison to the risks has been questioned.[72–74] Furthermore, there has not been a consensus on what degree of hypocapnia should be used to reduce the elevated ICP. In the past, P_{aCO_2} of less than 25 mm Hg was commonly used as a goal, whereas now it is not recommended that P_{aCO_2} decrease below 30 mm Hg. In a recent survey however, hyperventilation to a P_{aCO_2} less than 25 mm Hg was used in 29% of patients with elevated ICP.[72] Although an acute reduction in P_{aCO_2} does produce a rapid decrease in ICP, it also reduces cerebral blood flow, resulting in secondary damage from cerebral ischemia. Hence, the recommendation is that hyperventilation should be used only transiently (for example, while awaiting ventriculostomy placement), and that it be performed only with elevated ICP being confirmed by a pressure monitor and not empirically.[73]

Treatment

Correction of respiratory alkalosis is best performed by ameliorating the underlying cause, although in many cases

simple observation suffices. Hypoxia can be corrected with the administration of supplemental oxygen. Acetazolamide given prior to ascent or a slower ascent can help prevent or mitigate acute mountain sickness. Lastly, in the case of medications and mechanical ventilation, the offending drug should be stopped. Since changing the mode of ventilation from assist-control to synchronized intermittent mandatory ventilation does not improve respiratory alkalosis, sedation with or without paralysis may be required.

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Approach to Patients with Acid-Base Disorders

Jeffrey A Kraut MD and Nicolaos E Madias MD

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Systematic Approach to the Diagnosis of Acid-Base Disorders
Assessment of the Accuracy of the Acid-Base Measurements
History and Physical Examination
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Examination of Serum Electrolytes and Other Ancillary Laboratory Data
Measurement of Urine Electrolytes and pH
Illustrative Cases

Disorders of acid-base balance are commonly encountered in clinical practice and can have a substantial impact on the prognosis of the patient. Moreover, identification of a particular acid-base disturbance can provide a clue to an underlying disorder. Proper evaluation and treatment of acid-base disorders requires a systematic and analytic approach including: (1) assess the accuracy of the acid-base values using the Henderson equation or Henderson-Hasselbalch equation, (2) obtain a complete history and physical examination, (3) calculate the serum anion gap, (4) identify the primary acid-base disturbance and determine whether a simple or mixed disturbance is present, (5) examine serum electrolytes and additional laboratory data, and (6) measure urine pH and urine electrolytes and calculate the urine anion and osmolal gaps. Strict adherence to these principles will enable the clinician to diagnose the acid-base disturbance in the majority of cases. To illustrate these principles, 5 cases of patients with acid-base disturbances are analyzed. *Key words: acid-base disturbances, metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory alkalosis, anion gap, electrolytes.* [Respir Care 2001;46(4):392–403]

Introduction

Simple and mixed disturbances of acid-base balance are commonly encountered in ambulatory patients as well as in hospitalized patients. In both populations, recognizing the precise acid-base disorder(s) present is essential to appropriate treatment. Certain acid-base disorders can have a substantial impact on the patient's prognosis. Thus, severe acidemia due to metabolic acidosis, respiratory acidosis, or both can impair cardiovascular function and contribute to the development of life-threatening arrhythmias.[1,2] Similarly, severe alkalemia due to metabolic alkalosis, respiratory alkalosis, or both can contribute to the high mortality of patients in the intensive care unit.[3,4] Further, the finding of a particular acid-base disturbance can provide a clue to an underlying disorder: for example, respiratory alkalosis can precede overt signs of sepsis, and the combination of a high anion gap metabolic acidosis and respiratory alkalosis can suggest the diagnosis of salicylate intoxication.[5] In the following discussion we present our approach to the diagnosis of patients with disorders of acid-base balance. Although the approach is simple, it is sufficiently sound to allow rapid diagnosis of the prevailing acid-base disorders.

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Systematic Approach to the Diagnosis of Acid-Base Disorders

Proper evaluation and treatment of disturbances of acid-base balance requires the systematic and analytic approach outlined in Table 1. Adherence to these principles cannot be overemphasized. Even experienced physicians risk misdiagnosing the patient's acid-base status by bypassing this systematic approach.

One of the commonest errors clinicians make in the initial evaluation of patients with acid-base disorders is the incorrect use of acid-base terminology. Specifically, the suffix "*-osis*" is frequently used to imply changes in blood acidity, rather than the appropriate suffix, "*-emia*." Thus, acidosis indicates a pathophysiologic process tending to acidify body fluids, whereas acidemia indicates a reduction in blood pH. Similarly, alkalosis refers to the pathophysiologic process tending to alkalinize body fluids and alkalemia denotes an increase in blood pH. Importantly, patients can have acidosis or alkalosis without being acidemic or alkalemic, respectively. Given that it is the pH of the intracellular and extracellular compartments that affects organ function, rather than the absolute values of the determinants serum bicarbonate and arterial partial pressure of carbon dioxide (P_{aCO_2}),[5] it is essential to appropriately identify the abnormality in acid-base balance and indicate whether it gives rise to a deviation in blood acidity.

Table 1. Systematic Approach to the Analysis of Acid-Base Disorders

1. Assess the accuracy of the acid-base parameters using the Henderson equation: $[H^+] = 24 \times P_{CO_2}/[HCO_3^-]$ or the Henderson-Hasselbalch equation: $pH = 6.1 + \log[HCO_3^-]/0.03 \times P_{CO_2}$
2. Obtain a good history and perform a complete physical examination, looking for clues to a particular acid-base disturbance.
3. Calculate the serum anion gap: $[Na^+] - ([HCO_3^-] + [Cl^-])$
4. Identify the primary acid-base disturbance and assess whether a simple or mixed acid-base disturbance is present.
5. Examine serum electrolytes and ancillary laboratory data.
6. Measure urine pH and urine electrolytes, urine urea nitrogen, and glucose to calculate the urine anion gap ($[Na^+] + [K^+] - [Cl^-]$) or urine osmolal gap: measured osmolality − (2[$Na^+ + K^+$] + urea nitrogen/2.8 + glucose/18). Measurement of urine Na and Cl and urine pH should be obtained when metabolic alkalosis is present. Measurement of urine electrolytes, urine glucose and urea, and urine pH should be obtained when an element of normal anion gap metabolic acidosis is present.

P_{CO_2} = partial pressure of carbon dioxide
(From Kraut JA, Madias NE. Approach to the diagnosis of acid-base disorders. In: Massry SG, Glassock RJ, editors. Massry & Glassock's textbook of nephrology. Baltimore MD: Williams & Wilkins; 1995:487, with permission.)

Assessment of the Accuracy of the Acid-Base Measurements

The first step in analyzing any acid-base disorder is to ensure that the available measurements of pH, partial pressure of carbon dioxide (P_{CO_2}), and bicarbonate concentration are correct. The components of the bicarbonate-carbonic acid system are always at equilibrium in blood; therefore, measurements of pH, P_{CO_2}, and bicarbonate must adhere to the mathematical constraints of the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log [HCO_3^-]/(0.03 \times P_{CO_2})^{7,8} \quad (1)$$

pH and P_{CO_2} are measured with a blood gas analyzer using specific electrodes; serum bicarbonate is then derived by applying the known values for pH and P_{CO_2} into the Henderson-Hasselbalch equation. On the other hand, serum bicarbonate is determined in the chemistry laboratory using an autoanalyzer technique. In actuality, with this technique total CO_2 content is measured, but since serum bicarbonate normally comprises about 95% of that measurement, total CO_2 content can in practice be taken as equivalent to serum bicarbonate.

Routinely, venous blood is used for measurement of total CO_2 content, the resulting value being higher by 2–3 mmol/L than that of arterial blood. By contrast, arterial blood is usually employed for measurement of pH and CO_2 tension. Errors in accurate assessment of acid-base status can be introduced during the process of specimen collection or measurement of the acid-base variables. Blood should be collected anaerobically and serum promptly separated from whole blood and stored at 4° C until analyzed to ensure accurate assessment of acid-base equilibrium. The occurrence of spurious hypocapnia and hypobicarbonatemia resulting from the dilutional effect of excessive amounts of sodium heparin solution in the blood sample or failure to completely fill the vacutainer tube when obtaining blood has been emphasized.[9] Also, elevation of serum bicarbonate can occur after the blood is obtained if the serum is not immediately separated from the cells, since CO_2 continues to be generated by cellular metabolism.[10] More frequently, however, a decrease in serum bicarbonate of 3–5 mEq/L can be observed because of loss of CO_2 if the serum is left exposed to air for more than 90–120 minutes prior to the determination of CO_2.[10] Methodological errors are somewhat more frequent with the chemical determination of total CO_2. Thus, it is often more suitable to use pH, P_{CO_2}, and the derived plasma bicarbonate concentration to assess acid-base disorders.

Because of the risks of sampling arterial blood, including pain and thrombosis of arterial vessels, clinicians have explored the use of venous blood gas values to approxi-

mate arterial measurements of acid-base variables.[11] Although some studies have found a good correlation between routine acid-base measurements obtained from venous and arterial blood samples, other studies have failed to do so.[12] If patients have intact tissue perfusion, "arterialized blood" obtained by venipuncture after warming the dorsum of the hand to 41–43° C has been shown to approximate arterial blood gas samples relatively closely.[13] In selected patients this methodology might be used, but it requires strict attention to proper technique. At present we recommend the use of arterial blood for the assessment of the majority of patients with acid-base disorders.

Recently several investigators have recognized that, under conditions of reduced cardiac output and pulmonary perfusion but relative preservation of alveolar ventilation, arterial blood gas samples might not accurately reflect the acid-base milieu of cells.[14,15] Thus, in such patients mixed venous pH and P_{CO_2} were markedly different from the corresponding arterial values, pH being substantially lower and P_{CO_2} being substantially higher in mixed venous blood. Therefore, in critically-ill patients, mixed venous blood acid-base data can be helpful in detecting continuing impaired tissue perfusion. Of course, measurement of mixed venous blood gases necessitates the insertion of a central line and therefore will be done only in seriously ill patients in the intensive care unit.

Whenever independent measurements of the acid-base variables are available (ie, plasma bicarbonate concentration measured in the chemistry laboratory and pH and P_{CO_2} in the blood gas laboratory), the accuracy of the values can be checked using the logarithmic (Henderson-Hasselbalch) or linear (Henderson) form of the mass action equation for the bicarbonate-carbonic acid system.[7,8] As a matter of convenience, the linear form of the equation is more commonly employed to evaluate the accuracy of the acid-base variables:

$$[H^+] = 24 \times P_{CO_2}/[HCO_3^-] \quad (2)$$

where $[H^+]$ (the concentration of H^+ ions) is expressed in nEq/L, P_{CO_2} in mm Hg, and $[HCO_3^-]$ in mEq/L.[16] Conversion of pH into $[H^+]$ expressed in nEq/L can be accomplished by solving the equation $[H^+]$ = antilog (9 – pH). This interconversion is facilitated by the fact that the average normal arterial blood pH of 7.40 corresponds to a hydrogen ion concentration of 40 nEq/L. Furthermore, between pH values of 7.2 and 7.5, for every 0.1 unit change in pH, there is a change in hydrogen ion concentration of about 10 nEq/L in the opposite direction. Hydrogen ion concentration can also be derived from pH by sequentially multiplying the preceding hydrogen ion concentration by 0.8 when pH increases by 0.1, or by 1.25 when it decreases by 0.1. Also note that hydrogen ion concentration doubles for every 0.3 unit decrease in pH. The different methods of translating pH into hydrogen ion concentration are illustrated in Table 2. If a calculator is readily available, it is also convenient to use the logarithmic form of the mass action equation (Henderson-Hasselbalch) to accomplish the same purpose. If the independently measured values for pH, P_{aCO_2}, and bicarbonate concentration do not fit reasonably well into these equations, repeat determinations should be performed before any analysis of the nature of the acid-base disturbance is made.

Table 2. Comparison of Methods of Interconversion of pH and Hydrogen Ion Concentration with Actual Values

pH	Hydrogen Ion Concentration		
	Deduced Values (nEq/L)		Actual Values (nEq/L)
	A*	B†	
7.80	—	16	16
7.70	—	20	20
7.60	—	26	25
7.50	30	32	32
7.40	40	40	40
7.30	50	50	50
7.20	60	63	63
7.10	—	78	79
7.00	—	98	100
6.90	—	122	126

*A: Between pH 7.2 and 7.5, with every 0.1 unit change in pH, hydrogen ion concentration changes by 10 nEq/L in the opposite direction

†B: With every 0.1 unit increase in pH, multiply preceding hydrogen ion concentration by 0.8. With every 0.1 decrease in pH, multiply preceding hydrogen ion concentration by 1.25

(From Kraut JA, Madias NE. Approach to the diagnosis of acid-base disorders. In: Massry SG, Glassock RJ, editors. Massry and Glassock's textbook of nephrology. Baltimore MD: Williams & Wilkins; 1995:488, with permission.)

History and Physical Examination

After the internal consistency of the acid-base values has been verified, it is necessary to obtain a good history and to perform a complete and careful physical examination. These two tasks are often avoided in favor of immediate dissection of the laboratory data. In this regard it should be emphasized that a given set of acid-base values is never diagnostic of a particular acid-base disorder, but rather consistent with a wide range of acid-base abnormalities. Indeed, what appears to be a straightforward, simple acid-base disorder might in actuality reflect the composite of coexisting acid-base disturbances. Clues from the history and physical examination are therefore usually helpful in differentiating among the various possibilities. A patient with severe chronic renal failure or insulin-dependent diabetes mellitus might be expected to have a high anion gap metabolic acidosis. A patient with a history of vomiting or who is receiving diuretics might be expected

to have metabolic alkalosis. A patient with chronic lung disease might be expected to have respiratory acidosis. Similarly, a patient with a history of a disorder associated with extracellular volume depletion who presents with hypotension and evidence of reduced tissue perfusion might have lactic acidosis, whereas respiratory alkalosis is a likely possibility in a patient in hepatic coma. Physical abnormalities such as optic papillitis detected on funduscopic examination or evidence of severe respiratory distress and obstructive pulmonary disease detected by chest examination might suggest the presence of methanol intoxication or respiratory acidosis, respectively.

Calculation of the Serum Anion Gap

The serum anion gap is the sum of serum [Cl^-] and [HCO_3^-] subtracted from the sum of serum [Na^+] and [K^+].[17,21] Since the concentration of potassium in the serum is generally low and relatively constant, many experts ignore serum potassium concentration in this calculation. Defined in this way, [Na^+] – ([Cl^-] + [HCO_3^-]), the normal anion gap, which reflects primarily the negative charge of circulating proteins, ranges between 8 and 18 mEq/L, with an average of 10–12 mEq/L. A spurious increase in the anion gap can be observed if the serum sample is left exposed to air: loss of water and CO_2 results in a decrease in bicarbonate and increase in sodium, chloride, and potassium (the change is usually $\leq$ 6 mEq/L after 2 h).[17,18] Several clinical laboratories have introduced a new autoanalyzer method for measuring serum chloride that results in a higher value and, as a consequence, a lower level for the serum anion gap (average of 6–8 mEq/L).[20] Thus, in individual hospitals, the clinician should know the normal range of the serum anion gap in his or her laboratory when evaluating acid-base disorders. Moreover, given the wide range of the normal anion gap, if previous electrolyte values are available for the patient when no acid-base or electrolyte disturbance was present, the serum anion gap calculated from these electrolytes should be used as the baseline value. Because the level of serum proteins is a critical determinant of the level of the anion gap, a reduction in the anion gap will be seen in patients with hypoalbuminemia, the anion gap decreasing by approximately 2.5 mEq/L for every g/dL reduction in serum albumin concentration.[17,18] Other factors that can reduce the serum anion gap include presence of cationic paraproteins with multiple myeloma,[17] severe hypernatremia, hyperviscosity, and bromide intoxication.[18,21]

On the other hand, the anion gap can be modestly elevated with severe metabolic alkalosis, particularly if the alkalosis is chloride-sensitive, reflecting the increment in net anionic charge of circulating proteins, an increase in the concentration of these proteins, and an increase in the serum levels of organic acids.[21,22] However, even with severe alkalemia the increment in the anion gap is no more than 6 mEq/L, and therefore a greater value usually signifies the concomitant presence of a high anion gap metabolic acidosis. Importantly, in some circumstances an elevated serum anion gap might be the only clue to the presence of this acid-base disturbance. The increase in the serum anion gap occurs because the addition to the body fluids of any strong acid produces both a decrease in serum bicarbonate concentration and an increase in the concentration of the acid anion. If the acid accumulating in the blood is hydrochloric acid (as essentially occurs with bicarbonate loss from the body), the anion gap remains stable, because the decrease in serum bicarbonate is matched by an equivalent increase in serum chloride concentration. Actually, a slight decrease in serum anion gap might be observed that is presumed to reflect pH-related titration of proteins.[22–24] By contrast, if the acid accumulating in the blood is any acid other than hydrochloric acid (for example, lactic acid), the reduction in serum bicarbonate will be accompanied by an increase in the concentration of the acid anion, in this case lactate; serum chloride will remain unchanged. Since chloride and bicarbonate, but not lactate, are the anions considered in the calculation of the serum anion gap, an increase in the serum anion gap will be realized.

The nature of the reciprocal stoichiometry between the increase in the anion gap (termed the delta anion gap) and the decrease in serum bicarbonate (termed the delta bicarbonate) is controversial. Some experts have suggested that there is a strict 1:1 relationship: that is, the increase in the serum anion gap and decrease in serum bicarbonate concentration are equivalent.[17,18] Others have indicated that the ratio can range between 1 and 2 and may differ with different types of metabolic acidosis.[19,25] For example, some studies have suggested that the increase in serum anion gap exceeds the decrease in bicarbonate concentration in lactic acidosis of more than a few hours duration.[19] A feasible explanation for this phenomenon is that the space of distribution of hydrogen ions and lactate ions differs: hydrogen ions are buffered in both intracellular and extracellular compartments, whereas lactate anion is confined to the extracellular space. On the other hand, the delta anion gap/delta bicarbonate in diabetic ketoacidosis has been shown to more closely approximate 1:1: the loss of ketoacid anions with sodium or potassium in the urine lowers the anion gap and leads to an increase in serum chloride concentration without affecting serum bicarbonate concentration, thereby counteracting the impact of the differing spaces of distribution of protons and acid anions.[25,26] Whatever the nature of the relationship between the change in bicarbonate and serum anion gap, the addition of the value for the delta anion gap to the prevailing level of serum bicarbonate allows an approximation of the baseline value of plasma bicarbonate existing prior to the

development of the high anion gap metabolic acidosis. This exercise is important in distinguishing between a pure high anion gap metabolic acidosis and a mixed high and normal anion gap metabolic acidosis, and also in detecting the presence of a mixed high anion gap metabolic acidosis and metabolic alkalosis. As a corollary, a combined normal anion gap metabolic acidosis and metabolic alkalosis could not be detected merely by looking at the electrolytes, since the changes in electrolytes observed with these two disturbances mirror each other. Table 3 illustrates the utility of the delta gap in diagnosing such mixed acid-base disturbances. The magnitude of the anion gap noted with the various causes of metabolic acidosis can vary greatly; however, a level greater than 30–35 mEq/L is rare, except with lactic acidosis, ketoacidosis, and methanol or ethylene glycol intoxication.[18,27] Indeed, patients with these disorders have been reported with serum anion gaps exceeding 50 mEq/L.

Identification of the Primary or Dominant Acid-Base Disorder and Assessment of Whether a Simple or Mixed Acid-Base Disorder Is Present

Each of the cardinal acid-base disorders consists of the primary or initiating event and the secondary or adaptive response. Disorders initiated by a change in serum bicarbonate concentration, referred to as metabolic, elicit secondary changes in P_{aCO_2}. Similarly, disorders initiated by a change in P_{aCO_2}, referred to as respiratory, elicit secondary changes in the level of serum bicarbonate. Each of the secondary or adaptive responses has a characteristic time course and magnitude and tends to return blood pH toward, but not completely to normal levels.[28–31] The exception to this rule is chronic hypocapnia (respiratory alkalosis). If the hypocapnia is mild in degree, blood pH can be within normal limits.[31] Some degree of acidemia or alkalemia persists with all other acid-base disorders, as long as the initiating acidifying or alkalinizing process is present. Therefore, the presence of a normal blood pH in a patient with metabolic acidosis, metabolic alkalosis, or respiratory acidosis implies the presence of an additional disturbance.

Accurate assessment of disorders of acid-base equilibrium requires knowledge of both the time necessary for the adaptive responses to reach completion and the magnitude of the anticipated secondary adaptive response to each primary acid-base disorder. Table 4 shows the time course and magnitude of the secondary responses to the 4 cardinal acid-base disturbances. Analysis of disorders of acid-base equilibrium can also be aided by the use of an acid-base nomogram, an example of which is depicted in Figure 1. Such an acid-base map schematically presents the limits of compensation for each of the primary acid-base disturbances. Acid-base variables falling outside the expected range for each simple acid-base disorder denote the presence of a mixed acid-base disturbance. On the other hand, acid-base values falling within the expected range of a simple acid-base disorder are consistent with, but not diagnostic of, the particular disorder. Because the range of physiologic response to any simple disturbance is wide enough to allow the superimposition of another primary disturbance without shifting the acid-base equilibrium beyond the expected limits for a simple disorder, the simultaneous presence of several acid-base derangements can result in an acid-base profile that is identical to that produced by a simple acid-base disorder.

The clinician should also note that although each of the cardinal disturbances promptly activates a secondary response, the relationship between serum bicarbonate concentration and P_{aCO_2} for each of the primary disturbances has been empirically derived from data obtained during the steady state. Since a defined time interval is required

Table 3. Use of the Delta Anion Gap in the Diagnosis of Mixed Metabolic Acid-Base Disorders

Blood Chemistries	Normal	High Anion Gap Acidosis	High and Normal Anion Gap Acidosis	Metabolic Alkalosis	High Anion Gap Acidosis and Metabolic Alkalosis
Sodium (mEq/L)	140	140	140	140	140
Chloride (mEq/L)	106	106	114	94	94
Bicarbonate (mEq/L)	24	14	6	34	20
Δ Bicarbonate	—	10	18	10	4
Anion gap (mEq/L)	10	20	20	12	26
Δ Anion gap (mEq/L)	—	10	10	2	16
pH	7.40	7.29	7.10	7.50	7.38
P_{aCO_2} (mm Hg)	40	30	20	45	35

Δ = change.
P_{aCO_2} = arterial carbon dioxide tension.
(From Kraut JA, Madias NE: Approach to the diagnosis of acid-base disorders. In: Massry SG, Glassock RJ, editors. Massry & Glassock's textbook of nephrology. Baltimore MD: Williams & Wilkins; 1995:489, with permission.)

Table 4 Nature of Adaptive Response to Primary Acid-Base Disorders

Primary Acid-Base Disturbance	Initiating Mechanism	Secondary Physiologic Response	Time to Reach Completion	Limits of Compensation
Metabolic acidosis	↓ $[HCO_3^-]_p$	↓ P_{aCO_2} of 1–1.3 mm Hg for each mEq/L decrease in $[HCO_3^-]_p$ $P_{aCO_2} = 1.5 [HCO_3^-] + 8 \pm 2$	12–24 h	P_{aCO_2} of 10 mm Hg
Metabolic alkalosis	↑ $[HCO_3^-]_p$	↑ P_{aCO_2} of 0.4–0.7 mm Hg for each mEq/L increase in $[HCO_3^-]_p$	24–36 h	P_{aCO_2} of 55 mm Hg*
Respiratory acidosis	↑ P_{aCO_2}	Acute: ↑ $[HCO_3^-]_p$ of 1.0 mEq/L for every 10 mm Hg increase in P_{aCO_2}	5–10 min	$[HCO_3^-]_p$ of 30 mEq/L
		Chronic: ↑ $[HCO_3^-]_p$ of 3.5 mEq/L for every 10 mm Hg increase in P_{aCO_2}	72–96 h	$[HCO_3^-]_p$ of 45 mEq/L
Respiratory alkalosis	↓ P_{aCO_2}	Acute: ↓ $[HCO_3^-]_p$ of 2 mEq/L for every 10 mm Hg decrease in P_{aCO_2}	5–10 min	$[HCO_3^-]_p$ of 17–18 mEq/L
		Chronic: ↓ $[HCO_3^-]_p$ of 4–5 mEq/L for every 10 mm Hg decrease in P_{aCO_2}	48–72 h	$[HCO_3^-]_p$ of 12–14 mEq/L

P_{aCO_2} = arterial partial pressure of carbon dioxide
$[HCO_3^-]_p$ = plasma bicarbonate concentration.
*Rare cases with P_{aCO_2} values > 55 mm Hg have been reported.
(From Kraut JA, Madias NE: Approach to the diagnosis of acid-base disorders. In: Massry SG, Glassock RJ, editors. Massry & Glassock's textbook of nephrology. Baltimore MD: Wilhams & Wilkins, 1995:489, with permission.)

for the secondary response to reach completion, or to be eliminated once the primary disturbance has been corrected, a mixed acid-base disturbance might be incorrectly diagnosed, when only a simple disturbance is present, if insufficient time has elapsed for the secondary response to develop or resolve.

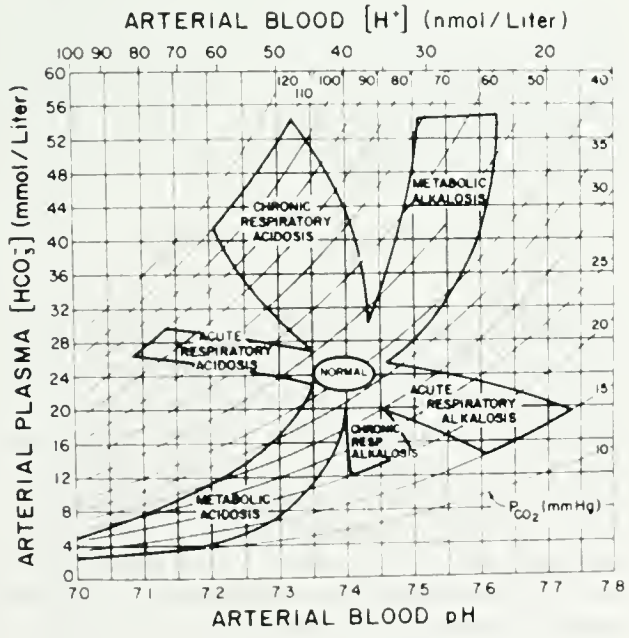

Fig. 1. Acid-base nomogram. This acid-base map depicts the 95% confidence limits of the normal metabolic and respiratory adaptation to each of the 4 primary acid-base disorders. (From Cogan M, Rector FC. Acid-base disorders. In: Brenner BM, Rector FC, editors. The kidney. Philadelphia: WB Saunders; 1986:473, with permission.)

To identify the primary or dominant acid-base disorder, we choose to first examine the serum bicarbonate concentration. Other experts have recommended examining blood pH first, but either approach is acceptable. An increase in serum bicarbonate can represent either metabolic alkalosis or the adaptive response to respiratory acidosis. If blood pH is elevated, metabolic alkalosis is the primary disorder; by contrast, if blood pH is reduced, then respiratory acidosis is the primary disorder. Conversely, a reduced serum bicarbonate concentration signifies metabolic acidosis or the adaptive response to respiratory alkalosis. If hypobicarbonatemia is accompanied by a reduced blood pH, metabolic acidosis is the primary disorder; on the other hand, an elevated blood pH in the presence of a low serum bicarbonate level indicates the presence of respiratory alkalosis. If blood pH is in the normal range in the company of hypobicarbonatemia or hyperbicarbonatemia, it indicates that metabolic and respiratory disturbances have an equivalent impact on acid-base balance and there is no dominant acid-base disorder. Assessment of whether a simple or mixed disturbance is present is then done by using the principles delineated above. An important clue to the presence of a mixed acid-base disorder is the deviation of serum bicarbonate and P_{aCO_2} in opposite directions, whereas in simple acid-base disturbances these values vary in the same direction. An additional clue to the presence of a mixed disorder is a normal or near-normal blood pH, signifying the coexistence of acid-base disorders with offsetting effects on blood pH. The sole exception to this rule, as noted above, is mild respiratory alkalosis: this acid-base disturbance can be present alone when the blood pH is within normal limits.

Examination of Serum Electrolytes and Other Ancillary Laboratory Data

In addition to the calculation of the serum anion gap, examination of the serum electrolytes, particularly serum potassium concentration, can be very helpful in the differential diagnosis of certain acid-base disorders, specifically normal anion gap (hyperchloremic) metabolic acidosis.[32,33] Normal anion gap acidoses can be conveniently divided into disorders in which serum potassium concentration is normal or elevated and those in which serum potassium concentration is low. The former disorders, typified by aldosterone deficiency or resistance, are characterized primarily by a renal defect in secretion of potassium and hydrogen,[32,34,35] whereas the latter group of disorders, typified by diarrhea, are distinguished by substantial losses of potassium during the generation and/or maintenance phases of the acidosis.[32] Therefore, identification of a normal anion gap metabolic acidosis should be followed by examination of the serum potassium concentration. By contrast, serum potassium concentration can be high, normal, or low in the various disorders associated with a high anion gap metabolic acidosis, and therefore is of no particular help in the differential diagnosis of this type of metabolic acidosis.[36] Hypokalemia accompanies all forms of metabolic alkalosis and is of no use in the diagnosis of this disorder. Respiratory acid-base disturbances can also alter serum potassium concentration, but the magnitude of these changes is generally much less than that noted with metabolic acid-base disturbances; therefore, in the absence of other explanations, marked deviations in serum potassium concentration usually suggest the presence of a metabolic acid-base disturbance.

In patients with high anion gap metabolic acidosis, determination of serum glucose, lactate, and creatinine concentrations and investigation for ketonemia or ketonuria will usually identify ketoacidosis, lactic acidosis, or renal failure as causes of the acidosis.[17–21,27] However, one should be cognizant of the fact that it might be impossible to fully account for the increase in the anion gap by measurement of identifiable organic acid anions or inorganic phosphate and sulfate.[18,27] In investigating for evidence of ketosis, it is important to remember that the nitroprusside reaction detects acetoacetate rather than the more predominant beta-hydroxybutyrate species. Particularly in alcoholic ketoacidosis or combined lactic acidosis and diabetic ketoacidosis there is a shift away from the formation of ketoacetate toward beta-hydroxybutyrate, and therefore the nitroprusside reaction can be negative or only mildly positive. A screen of blood or urine for certain toxins is very useful (see below) in detecting aspirin, methanol, or ethylene glycol intoxication. In this regard, measurement of serum osmolality and comparison of this value to the estimate of serum osmolality derived from consideration of the usual osmotically active substances in blood can be of great value in suggesting the diagnosis of toxic alcohol intoxications.[37] Under normal circumstances, the quantitatively most important moieties contributing to serum osmolality are sodium (and its counterbalancing anions, chloride and bicarbonate), glucose, and urea. Thus, serum osmolality can rapidly be estimated using the following formula:

$$2 \times [Na^+] + [\text{glucose}]/18 + [\text{BUN}]/2.8 \quad (3)$$

wherein [glucose] and blood urea nitrogen ([BUN]) are expressed in mg/dL. An osmolal gap (defined as the difference between the measured and estimated serum osmolality) greater than 10 mOsm/kg H_2O signifies the presence in serum of additional osmotically active particles and suggests the diagnosis of methanol or ethylene glycol intoxication, or alcoholic ketoacidosis. A mildly increased osmolal gap has been identified in some patients with lactic acidosis or chronic renal failure, the explanation for which remains unclear.[38–40] Thus, in some instances an osmolal gap increased to values as high as 20 mOsm/kg H_2O might not indicate toxic alcohol ingestion. On the other hand, methanol or ethylene glycol intoxication can be found in the presence of only a trivial increment in the osmolal gap, particularly if this measurement is obtained many hours after the intoxication, a time when these alcohols might have been largely metabolized to their toxic byproducts.[41] The severity of the acidemia can also be helpful in distinguishing among the many diagnostic possibilities. Severe acidemia (pH < 7.00) is most common with diabetic ketoacidosis, lactic acidosis, and methanol or ethylene glycol intoxication, but is uncommon with other causes of metabolic acidosis.[27]

Measurement of Urine Electrolytes and pH

In addition to the 5 steps discussed thus far, measurement of urinary electrolytes and pH, and calculation of the urinary anion or osmolal gap can provide critical information for the differential diagnosis of metabolic alkalosis and normal anion gap metabolic acidosis.[42–45] By contrast to metabolic acidosis, the electrolyte profile in metabolic alkalosis is identical in all forms, being characterized by a reciprocal increase in bicarbonate concentration and decrease in chloride concentration.[46,47] Therefore, serum electrolytes are of no value in the differential diagnosis of this disorder. However, measurement of urine electrolytes, particularly chloride and sodium concentrations, can be a valuable tool in the differential diagnosis of metabolic alkalosis.[46] On the basis of measurement of urine chloride, the metabolic alkaloses can be divided into chloride-responsive (low urine chloride concentration, < 20/mEq/L) and

chloride-resistant (high urine chloride concentration, > 20 mEq/L) forms. If a measurement of urine chloride concentration is not readily available, measurement of urine Na^+ along with that of urine pH can provide similar information to allow assignment to either one of these categories of metabolic alkalosis. Thus, all patients with chloride-responsive forms of metabolic alkalosis will not only have a low urine chloride concentration, but usually a low urine Na^+ concentration, reflecting a sodium and chloride-avid state. An exception to this rule is seen in individuals with metabolic alkalosis due to vomiting or gastric drainage who are observed during the "disequilibrium" phase. In this early phase of vomiting or gastric drainage, urine Na^+ concentration can be high, but, if so, it will be accompanied by elevated pH, reflecting the increased quantities of bicarbonate appearing in the urine.[47] Of course, if renal tubular reabsorption of sodium and chloride is compromised by other factors (such as renal tubular damage, the excretion of nonreabsorbable anions, or osmotic diuresis), measurement of urine electrolyte excretion can be misleading.[44] Determination of urine electrolytes can also be helpful in distinguishing among the various causes of normal anion gap metabolic acidosis. Low urine sodium and potassium concentrations are found with diarrhea, high levels of sodium and potassium are found in proximal and distal renal tubular acidoses, and high sodium and low potassium excretion can be indicative of aldosterone deficiency or resistance.[32,42,44]

Renal and extrarenal disorders can cause normal anion gap acidosis. Although clinical data and routine laboratory studies are usually sufficient to ascertain the cause of the acidosis, estimation of the urine ammonium excretion can be helpful in determining if impaired renal acid excretion is a causative factor: urine ammonium excretion is generally increased 4–5-fold with metabolic acidosis of extrarenal origin.[32,45] Because urine ammonium excretion is not easily measured in most clinical laboratories, urine electrolytes can be used to calculate the urine anion gap (defined as $[Na^+] + [K^+] - [Cl^-]$), which grossly estimates urine ammonium excretion.[44,48,49] Requirements for its use are that the urine does not contain unusual anions (eg, ketone bodies, carbenicillin) and that bicarbonate excretion is low (urine pH < 6.5). Ammonium is an unmeasured cation, so an increase in its excretion as NH_4Cl will cause an increase in the urine Cl^- excretion and a negative value for the urine anion gap: that is, $[Cl^-]$ exceeding the sum of $[Na^+]$ and $[K^+]$. A negative urine anion gap indicates that the urine contains substantial quantities of ammonium and is evidence against an impairment in ammonium excretion as the major factor in the pathogenesis of the acidosis. On the other hand, a positive value in the range of 20–30 mEq/L indicates that ammonium excretion is low and implicates a reduction in ammonium excretion as an important factor in the production of metabolic acidosis.

Despite adequate quantities of ammonium being present in the urine, a positive urine anion gap can be seen when there is increased excretion of unusual unmeasured anions such as beta-hydroxybutyrate and acetoacetate, as with ketoacidosis, or hippurate with toluene intoxication.[33,44,50–52] These anions obligate the excretion of sodium and potassium, producing the positive anion gap. Under these circumstances, urine ammonium excretion can be estimated from calculation of the urine osmolal gap. The urine osmolal gap is defined as

$$\text{measured osmolality} - (2[Na^+ + K^+] + [\text{urea nitrogen}]/2.8 + [\text{glucose}]/18) \quad (4)$$

wherein [urea nitrogen] and [glucose] are measured in mg/dL. The gap between the measured and calculated urine osmolality should primarily reflect excretion of ammonium salts. Importantly, the calculation will not be affected by urine excretion of unusual anions, since they will be accounted for by the accompanying cations: sodium, potassium, and ammonium. An appropriate urine osmolal gap in an acidotic patient is greater than 150–200 mOsm/kg H_2O, whereas, in patients with low ammonium excretion, the urine osmolal gap is usually less than 50–100 mOsm/kg H_2O.[44,45,52] The ammonium excretion is one half of the calculated osmolal gap, the residual half being accounted for by the accompanying anions.

Finally, measurement of urine pH in individuals with normal anion gap metabolic acidosis, along with an estimation of urinary ammonium excretion, can aid in the detection and/or further characterization of metabolic acidosis resulting from defects in renal acidification.[32,34,35,48] A sample of urine is obtained under oil for measurement of pH and ammonium when the patient is acidemic. If the urine pH is < 5.5, bicarbonate is administered until the urine becomes alkaline or the serum bicarbonate returns to normal. The development of an alkaline urine (pH > 6.5) prior to normalization of serum bicarbonate indicates that proximal renal tubular acidosis is present. If the urine remains acidic, it indicates that other disorders, such as diarrhea, might underlie the acidosis. If urine pH is high (> 6.0) and remains relatively constant during bicarbonate administration, distal renal tubular acidosis is present. Measurement of urine ammonium or estimation of its quantity (using the urine anion or osmolal gap) can help differentiate between those nonrenal disorders in which ammonium excretion is increased and those forms of renal acidosis, such as aldosterone deficiency or resistance, in which urine pH can be variable but ammonium excretion is decreased.[32]

In summary, use of the steps outlined in Table 1 and discussed in some detail in the text provides a rational approach to the diagnosis of acid-base disorders. The use of these principles will be illustrated in the following case reports. For the purposes of these reports, the following

mean normal values for blood acid-base variables were used: pH 7.40, hydrogen ion concentration 40 nEq/L, P_{aCO_2} 40 mm Hg, serum bicarbonate concentration 24 mEq/L, and serum anion gap 10 mEq/L.

Illustrative Cases

Case 1

A 60-year-old man with a history of chronic alcoholism was admitted to the hospital with a history of abdominal pain and decreased mental status. The patient had a long history of alcohol ingestion and several bouts of alcoholic hepatitis. He was presently receiving no medication. Physical examination on admission revealed blood pressure of 130/80 mm Hg while supine and upright. His pulse was 100 beats per minute and regular. Respirations were 26 per minute and unlabored. The chest was clear to auscultation and percussion. Cardiac examination revealed no murmurs or gallops. Examination of the abdomen revealed a slightly enlarged liver but no evidence of ascites. Laboratory data obtained on admission revealed: Na^+ 136 mEq/L, K^+ 3.2 mEq/L, HCO_3^- 12 mEq/L, Cl^- 100 mEq/L, BUN 22 mg/dL, creatinine 1.4 mg/dL, glucose 100 mg/dL, pH 7.35, and P_{aCO_2} 34 mm Hg. Serum osmolality was 320 mOsm/kg H_2O. Urine ketones were negative.

At first perusal of the data, it appears the patient has a mixed acid-base disturbance: metabolic acidosis and respiratory acidosis. The serum bicarbonate and blood pH were both reduced, indicating the presence of metabolic acidosis. The P_{aCO_2} is inappropriately high for the degree of hypobicarbonatemia, indicating that an element of respiratory acidosis is also present.

However, a check of the internal consistency of the data revealed that the measured bicarbonate concentration is substantially lower than the value calculated from the pH and P_{aCO_2} using the Henderson or Henderson-Hasselbalch equations.

$$[H^+] = 24 \times P_{aCO_2}/HCO_3^-$$

Inserting the measured and calculated values, we have

$$45 = 24 \times 34/HCO_3^-$$

And HCO_3^- is calculated by

$$24 \times 34/45 = 18 \text{ mEq/L}$$

Indeed, a repeat measurement of serum bicarbonate concentration revealed a value of 17 mEq/L. Despite the higher serum bicarbonate concentration, the patient still had a high anion gap metabolic acidosis. However, the P_{aCO_2} is now appropriate to the level of serum bicarbonate, indicating the patient has a simple metabolic acidosis. Measurement of serum osmolality by freezing point depression had revealed an osmolality of 320 mOsm/kg H_2O, substantially higher than the value calculated from the concentrations of sodium, potassium, urea, and glucose (ie, 285 mOsm/kg H_2O). A disparity of this degree between the measured and estimated osmolality indicates that an osmotically active particle has accumulated in the blood. A toxin screen of the blood revealed elevated levels of methanol consistent with methanol intoxication. Rapid diagnosis of this entity is essential, as death can ensue rapidly. The patient was treated with an alcohol infusion to lessen the metabolism of methanol to its toxic byproducts, and with dialysis to remove the methanol. He made a rapid recovery.

This case illustrates the importance of establishing the internal consistency of the acid-base data before making a diagnosis of the acid-base disorder(s) present.

Case 2

A thin, 42-year-old woman is seen in the clinic complaining of muscle cramps and weakness. She denied abdominal pain, nausea, or vomiting. She reported taking no medication. Physical examination revealed a blood pressure of 120/80 mm/Hg while supine and upright, pulse was 65 beats per minute, and respirations were 12 per minute and unlabored. The rest of the physical examination was unremarkable except for a short systolic murmur at the apex. Laboratory data revealed: Na^+ 140 mEq/L, K^+ 2.5 mEq/L, Cl^- 94 mEq/L, HCO_3^- 32 mEq/L, BUN 18 mg/dL, creatinine 0.9 mg/dL, pH 7.49, P_{aCO_2} 44 mm Hg. Urine electrolytes: Na^+ 40 mEq/L, Cl^- 60 mEq/L, pH 6.0.

The elevated plasma bicarbonate concentration and blood pH signify the presence of metabolic alkalosis. The P_{aCO_2} is appropriately elevated for this degree of hyperbicarbonatemia (change in P_{aCO_2} of 0.5 × change in bicarbonate), indicating the development of appropriate respiratory adaptation. Although the serum anion gap is slightly elevated (a delta anion gap of 4 mEq/L), this slight increment probably does not reflect a coexisting high anion gap metabolic acidosis. A small increase in the anion gap (not exceeding 6 mEq/L) is observed in patients with moderate to severe metabolic alkalosis. The cause of the metabolic alkalosis is not immediately obvious, since the patient denied taking any medications (such as diuretics). Urine chloride and sodium were both elevated, excluding surreptitious vomiting and other forms of chloride-responsive metabolic alkalosis. The elevated urine chloride concentration is consistent with chloride-resistant metabolic alkalosis. The patient did not have an elevated blood pressure, a clinical finding that would appear to exclude most mineralocorticoid-excess syndromes. Diuretic administration could pro-

duce this picture. Diuretic administration is generally thought to produce a chloride-responsive form of metabolic alkalosis; indeed, correction of the alkalosis can be easily achieved by administration of sodium or potassium chloride after discontinuation of the diuretic. However, these patients can have low or high urine chloride and sodium concentrations depending on how soon urine electrolytes are measured after diuretic administration. However, this diagnosis was essentially excluded by a negative screen for diuretics. The serum potassium concentration was substantially reduced, but not to the degree to produce metabolic alkalosis by itself. Bartter's or Gitelman's syndrome, two disorders associated with mutations in the Na^+-K^+-$2Cl^-$ and thiazide-sensitive Na^+–Cl^- cotransporter, respectively, could account for this clinical picture. Indeed, analysis of relatives revealed other individuals with a similar picture, and genetic analysis revealed evidence of a mutation in the Na^+–Cl^- cotransporter, suggestive of Gitelman's syndrome. This case illustrates the utility of urine electrolyte measurements in the evaluation of metabolic alkalosis.

Case 3

A 40-year-old woman with a history of sarcoidosis was seen in the emergency room with nausea, vomiting, and abdominal pain several days after developing a sore throat and fever. Physical examination on admission revealed the blood pressure to be 135/60 mm Hg while supine and upright. Pulse was 110 beats per minute, respirations were 22 per minute, and temperature was 39.5° C. The chest was clear to percussion and auscultation. There were no murmurs or gallops. Laboratory data included: Na^+ 140 mEq/L, K^+ 3.9 mEq/L, HCO_3^- 10 mEq/L, Cl^- 105 mEq/L, pH 7.14, P_{aCO_2} 30 mm Hg, glucose 600 mg/dL, BUN 9 mg/dL, creatinine 1.6 mg/dL, and urine and blood ketones were both positive. Microscopic examination of the urine was negative. The patient was admitted to the intensive care unit and given insulin and normal saline, but no base replacement. Two days later, repeat electrolytes revealed: Na^+ 135 mEq/L, K^+ 3.9 mEq/L, HCO_3^- 12 mEq/L, Cl^- 114 mEq/L, pH 7.25, P_{aCO_2} 28 mm Hg, glucose 600 mg/dL, BUN 9 mg/dL, creatinine 1.3 mg/dL, and urine and blood ketones were both slightly positive.

The initial acid-base values are consistent with a combination of metabolic and respiratory acidosis. Both the blood pH and serum bicarbonate concentration are reduced, indicative of metabolic acidosis. The P_{aCO_2} is inappropriately elevated for the magnitude of the hypobicarbonatemia, indicating this patient also has some degree of respiratory acidosis. Given a serum bicarbonate concentration of 10 mEq/L, a change of 14 mEq/L, one would anticipate the P_{aCO_2} should have decreased by 14–18 mm Hg, to 22–26 mm Hg. In fact, the P_{aCO_2} was substantially higher, indicating that some other process was attenuating ventilation, thereby preventing the expression of the appropriate respiratory response to metabolic acidosis. A chest radiograph revealed bilateral pneumonia. Examination of the serum electrolytes and calculation of the ratio of the delta anion gap to delta bicarbonate indicates that a high anion gap metabolic acidosis is primarily present, since the change in anion gap (15 mEq/L) and change in serum bicarbonate concentration (14 mEq/L) were virtually identical. In diabetic ketoacidosis the delta anion gap/delta bicarbonate approximates one. However, after two days of treatment the acidosis has been converted into a normal anion gap (hyperchloremic) metabolic acidosis, since serum bicarbonate rose only slightly (2 mEq/L), but the anion gap fell to normal (9 mEq/L). A normal anion gap metabolic acidosis is not uncommon at the time of presentation of diabetic ketoacidosis and becomes more prevalent during the course of treatment with insulin and normal saline.[26] Since the latter form of metabolic acidosis will not correct rapidly and might require administration of base, it is essential to detail the exact nature of the metabolic acidosis present in patients with presumed diabetic ketoacidosis. This case highlights the importance of calculating the serum anion gap in all patients with acid-base disorders.

Case 4

A 66-year-old man with a history of chronic obstructive lung disease for many years was seen in the clinic complaining of increasing shortness of breath and swelling in his feet. Chest examination revealed diminished breath sounds and diffuse wheezing. There was 2+ to 3+ pretibial edema. Laboratory data were as follows: Na^+ 136 mEq/L, HCO_3^- 28 mEq/L, K^+ 4.0 mEq/L, Cl^- 96 mEq/L, pH 7.26, P_{aCO_2} 64 mm Hg, and arterial partial pressure of oxygen 60 mm Hg (on room air).

A diagnosis of acute exacerbation of lung disease and right-sided heart failure was made, and he was prescribed a low salt diet, diuretics, steroids, and antibiotics. He was asked to return to the clinic in 2 days for reevaluation. Physical examination on the next visit revealed blood pressure 130/80 mm Hg while supine and upright, pulse 100 beats per minute, respirations 14 per minute, and temperature 37.0° C. Examination of the chest revealed bilateral wheezes. Examination of the heart showed an S_3 gallop at the apex. Examination of the extremities revealed 1+ pretibial and pedal edema. Laboratory data were as follows: Na^+ 130 mEq/L, HCO_3^- 34 mEq/L, K^+ 3.0 mEq/L, Cl^- 86 mEq/L, pH 7.40, P_{aCO_2} 56 mm Hg, and arterial partial pressure of oxygen 72 mm Hg (on room air).

The initial set of acid-base values is consistent with either acute respiratory acidosis superimposed upon chronic respiratory acidosis or the combination of chronic respiratory acidosis and metabolic acidosis. With acute respi-

ratory acidosis, for every acute increase of P_{aCO_2} of 10 mm Hg, serum bicarbonate concentration increases by 1 mEq/L. By contrast, with chronic respiratory acidosis, for every chronic increase of P_{aCO_2} of 10 mm Hg, serum bicarbonate concentration increases by 3–4 mEq/L. In the chronic setting, the increase in serum bicarbonate is caused both by titration of nonbicarbonate buffers and stimulation of net acid excretion by the kidney. The acute adaptation is complete within minutes, whereas the chronic adaptation takes 3–5 days before it reaches completion. An individual who chronically maintained a P_{aCO_2} of 64 mm Hg would be expected to have a serum bicarbonate concentration of approximately 31–33 mEq/L. In this patient, the increase in serum bicarbonate and hydrogen ion concentration is less than expected for someone with a chronic P_{aCO_2} level of 64 mm Hg. There was no history to suggest any causes of metabolic acidosis, and other laboratory studies excluded any element of metabolic acidosis. Subsequent review of previous medical records indicated that the patient usually maintained a P_{aCO_2} of approximately 50 mm Hg; thus, it is likely the patient has acute respiratory acidosis superimposed upon chronic respiratory acidosis.

The second set of acid-base values is consistent with the combined presence of chronic respiratory acidosis and metabolic alkalosis. The normal blood pH is an important clue to the coexistence of two primary acid-base disturbances: with the exception of mild respiratory alkalosis, single primary acid-base disturbances are associated with an abnormal blood pH. In this instance, respiratory acidosis and metabolic alkalosis had divergent effects on blood acidity, resulting in a normal blood pH. The serum bicarbonate is higher than anticipated for an individual with a chronic P_{aCO_2} of 56 mm Hg, indicating the coexistence of metabolic alkalosis. The metabolic alkalosis in this patient was produced largely by the administration of diuretics and a low salt diet given for the treatment of right-sided heart failure. Although the development of metabolic alkalosis might have been expected to suppress ventilation, thereby resulting in a further increase in P_{aCO_2}, the treatment of the lung disease with antibiotics and steroids and treatment of the congestive heart failure with diuretics actually led to some slight improvement in pulmonary function and therefore a decrease in P_{aCO_2}.

Case 5

A 45-year-old alcoholic man was admitted to the hospital because of an alteration in mental status and increased abdominal girth. Medications on admission included furosemide and spironolactone. Physical examination revealed a cachectic and icteric man who was extremely lethargic. Blood pressure was 100/60 mm Hg while supine and 80/50 mm Hg while upright. Pulse was 90 beats per minute and regular. Respirations were 22 per minute. The lungs were clear to auscultation and percussion. Examination of the heart revealed no murmurs or gallops. The abdomen was protuberant, and there was evidence of ascites as manifested by a fluid wave. There was 1+ pretibial edema. Laboratory data on admission revealed: Na^+ 126 mEq/L, K^+ 3.0 mEq/L, HCO_3^- 22 mEq/L, Cl 80 mEq/L, BUN 10 mg/dL, creatinine 0.9 mg/dL, bilirubin 16 mg/dL, albumin 2.5 g/dL, serum glutamic-oxaloacetic transaminase (SGOT) 150 international units, pH 7.45, and P_{aCO_2} 32 mm Hg.

At first glance, the acid-base values are consistent with chronic hypocapnia (chronic respiratory alkalosis), since mild hypobicarbonatemia and hypocapnia are present and blood pH is slightly elevated. Indeed, chronic hypocapnia is common in patients with decompensated liver disease. Calculation of the serum anion gap, however, revealed it to be elevated to 24 mEq/L, a change not typically observed with respiratory alkalosis, but indicative of metabolic acidosis. Furthermore, addition of the delta anion gap of 14 mEq/L to the prevailing serum bicarbonate concentration of 22 mEq/L revealed that the patient's serum bicarbonate had been 36 mEq/L. The metabolic alkalosis was presumably the consequence of diuretic administration. Therefore, this patient had both metabolic alkalosis and high anion gap metabolic acidosis. Perusal of the serum electrolytes alone, without calculating the serum anion gap, would have failed to detect this complex acid-base disturbance. This case illustrates the importance of calculating the serum anion gap in every acid-base disorder presented to the physician. Examination of the P_{aCO_2} relative to the prevailing bicarbonate concentration of 22 mEq/L revealed hyperventilation in excess of the normal adaptive response to metabolic acidosis, indicative of a coexisting respiratory alkalosis. Thus, this patient had a triple acid-base disturbance. Triple acid-base disturbances are common in seriously ill patients, particularly those with chronic liver disease.

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Books, Films, Tapes, & Software

Fluid, Electrolyte, and Acid-Base Physiology: A Problem-Based Approach, 3rd edition. Mitchell L Halperin MD and Marc B Goldstein MD. Philadelphia: WB Saunders. 1999. Soft-cover, illustrated, 532 pages, $59.95.

The authors grouped this book's contents into 4 major sections, starting off with acid-base, then sodium and water, then potassium, and concluding with hyperglycemia. In addition, the book includes a separate table of contents listing the case studies and flow charts. Unfortunately, the section on electrolyte is limited to sodium and potassium only.

The section on acid-base consists of 5 chapters, covering principles of acid-base physiology, clinical approach to acid-base, metabolic acidosis, metabolic alkalosis, and respiratory acid-base disturbances. The section on sodium and water covers sodium and water physiology, hyponatremia, and hypernatremia. The section on potassium contains chapters on potassium physiology, hypokalemia, and hyperkalemia. The section on hyperglycemia covers solely hyperglycemia. Each chapter is preceded by its table of contents for easy exploration of a specific topic. The chapter begins with a list of objectives, an outline of major principles, and an introductory case, which is discussed in detail at the end of the chapter, with questions and answers. Each chapter provides the basic physiology and biochemical reactions, followed by clinical approach or diagnostic studies, specific disorders or etiologies, treatment, and illustrations of cases with pertinent questions and answers. The authors include a list of suggested readings under specific topics and an index at the end of the book.

This book is directed at several levels of readership: those faced with an emergency, those who are looking for a quick review, those facing a clinical challenge, and those who wish to become experts. However, because of the extensive background in basic science, this book is appropriately directed to physicians, physicians-in-training, and medical students.

This book aims to bring the basic science concepts of 3 interrelated areas (fluid, electrolyte, and acid-base physiology) to the bedside as seen in the day-to-day practice of medicine. The authors highlight these concepts with numerous flow charts, figures, and case studies. This book is very practical from the standpoint of a "problem-based approach." In addition, it is up to date, with discussions of mechanisms operating at the subcellular level.

On the whole, the book is a tremendous success. Its strength lies in the understanding at the basic science level and its direct application at the bedside, with lists of possible etiologies, clinical approach, and treatment. At the end of each chapter, problem-oriented case illustrations serve to highlight the important points discussed and the experience of the authors. Each chapter is very well written and important principles are highlighted in shaded boxes. By and large the references are current, but with retention of classic articles.

The difficulty I have with this book is the extensive use of abbreviations. Interpreting the abbreviations is a daunting task for a reader who wishes only to review the problem-oriented cases, because the reader must scan through the preceding pages to decipher the abbreviations, some of which cannot be easily inferred: for example, "NAE" for "net acid excretion" and "NHE" for "sodium hydrogen exchanger." It would be very helpful if the authors would provide a list of abbreviations in an appendix, for easy reference.

In summary, the authors have achieved their goal of bringing basic science concepts to bedside application. They have provided a practical approach in the management of patients with acid-base disorders and fluid, sodium, and potassium disturbances. This book can be used as a reference for clinicians—at all levels of experience—taking care of patients in emergency rooms, intensive care units, medical, or surgical inpatient areas.

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Handbook of Fluid, Electrolyte, and Acid-Base Imbalances. Joyce LeFever Kee RN MS and Betty J Paulanka RN EdD. Albany, New York: Delmar Publishers. 2000. Softcover, illustrated, 320 pages, $26.95.

This paperback was developed from a parent text, *Fluids and Electrolytes with Clinical Applications: A Programmed Approach,* and according to the authors is designed to be used either with the parent text or as a stand-alone resource. The book is designed for use by all clinicians and contains numerous diagrams and tables in support of (and as a summary of) the material being presented. The book is organized into 5 units composed of 19 chapters.

Unit I discusses the influence of fluids on the body. The factors that control the retention, elimination, and movement of fluids across membranes are presented. Separate chapters are dedicated to extracellular fluid volume deficit, extracellular fluid volume excess, extracellular fluid volume shift, and intracellular fluid volume excess. Each of these topics is addressed from the standpoints of pathophysiology, etiology, clinical manifestations, clinical management, and client management.

Unit II covers electrolytes and their effects on the body. Potassium, sodium, chloride, calcium, magnesium, and phosphorus are discussed. Each are presented using the discussion template of pathophysiology, etiology, clinical manifestations, clinical management, and client management. Tables are used extensively to organize pertinent information.

Unit III deals with acid-base balance and imbalance. The regulatory mechanisms that control pH, including compensation and correction, are discussed. The common respiratory and metabolic disturbances are then discussed again, using pathophysiology, etiology, clinical manifestations, clinical management, and client management as the format.

Unit IV covers intravenous therapy. Basic classification of intravenous solutions and the various types of fluids for intravenous administration are discussed prior to the presentation of intravenous administration and total parenteral nutrition. The pur-

pose of intravenous therapy, calculations for intravenous infusion, and possible complications are among the topics discussed. Client management, including assessment, diagnoses, interventions, and evaluation and outcomes, are also presented.

Unit V deals with fluid, electrolyte, and acid-base imbalances in clinical situations. Chapters related to acute disorders (trauma and shock), gastrointestinal surgical interventions and chronic diseases such as heart failure, diabetic ketoacidosis, and chronic obstructive pulmonary disease are included. The fluid problems of infants, children, and older adults are also addressed.

The 7 appendixes address and/or list: clinical pathways for congestive heart failure and children with fluid and electrolyte imbalances; summary of acid-base imbalances; clinical problems associated with fluid imbalances; clinical problems associated with electrolyte imbalances; foods rich in potassium, sodium, calcium, magnesium, chloride, and phosphorous; and common laboratory tests and values for adults and children.

In general, I found this paperback easy to read, with a pleasant appearance and numerous reference tables that summarized the material being discussed. Each of the concepts is presented clearly and concisely, and although most explanations are adequate, some require prior exposure to the topic. For example, the discussion in Unit III of the regulatory mechanisms of pH control introduces the concept of buffer systems as "those that maintain the acid-base balance of body fluids by protecting the fluids against changes in pH." There are specific examples of the major body buffers, along with their chemical action listed in the accompanying table (U3–2), but one would need a prior understanding of how buffers work in order to appreciate the description provided. I think those clinicians who might purchase this text (eg, physicians, respiratory therapists, and nurses) would have the necessary background, but I question the authors' assertion that the book can be used as a stand-alone product.

The specific topics selected and the organization of material are appropriate and logically sequenced. Several topic discussions and accompanying figures, however, are somewhat confusing. For example, in an effort to simplify the concept of the factors that influence the movement of fluids across membranes, the authors have misstated that concept. In Unit I, in the discussion of fluid pressures (Starling's law), it is stated that because there is a hydrostatic pressure gradient in the arteriolar end of a capillary in the direction of the interstitial space, then fluid will move out of the capillary. It is further stated that, because there is a plasma colloid osmotic pressure gradient in the direction of the venular end of the capillary, then fluid will move from the tissues into the capillary. Starling's law states that it is the net of these 4 forces working together at any point in the capillary bed system that determines whether or not we have net fluid movement in or out of a particular fluid compartment. In other words, if the net difference between the hydrostatic pressures in the capillary and tissue and the colloid osmotic pressures in the capillary and tissue is positive, then fluid will move out of the capillary, and if it is negative, then fluid will move in. I also found the accompanying figure, U1–2, to be confusing.

In Unit I, Chapter 2, under the heading "Pathophysiology," the reader is referred to Figure 2–1, which is supposed to differentiate between iso-osmolar and hypo-osmolar fluid volume excess. Both illustrations in this figure are labeled as "Normal – fluid percent of body weight" and make no reference to which is iso-osmolar and which is hypo-osmolar.

In Unit II, Figure U2–1 illustrates, by use of bar graphs, the relative amounts of anions and cations present in both extracellular and intracellular fluid compartments. The relative size of the bar graph compartments is not reflective of the relative concentration of some of the electrolytes. Specifically, extracellular fluid bicarbonate and phosphate concentrations are illustrated as being of equal concentration, but have concentrations of 27 mEq/L and 2 mEq/L, respectively. Similarly, the intracellular fluid chloride concentration is illustrated on the bar graph as being greater than the bicarbonate concentration, although the stated concentrations are 1 mEq/L and 10 mEq/L, respectively.

In Unit II, Table 6–3, which summarizes chloride and its functions, states that "the kidneys excrete the anion chloride or bicarbonate, and *sodium reabsorbs* either chloride or bicarbonate to maintain the acid-base balance." The reabsorption of sodium in the kidney is accompanied by both chloride and bicarbonate ion. The mechanism by which each is reabsorbed is different, dependent on concentration, and in general responds to electrolyte imbalance in the body. Sodium of course does not *reabsorb* either of these ions but does accompany them as they enter peritubular plasma.

The above criticisms should not detract from the fact that this is a very well written reference text with many valuable tables that summarize the material discussed. Each chapter is organized to assist the reader in clinical application of the material. The references are extensive and current, and the index is quite detailed and accurate. I do feel that this is a useful clinical reference text that could be carried in a lab coat if one desired, but in any case would be useful on a daily basis. I would recommend it as an addition to one's library.

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Hyperbaric Medicine Practice, 2nd edition. Eric P Kindwall MD and Harry T Whelan MD, editors. Flagstaff, Arizona: Best Publishing, 1999. Hardcover, illustrated, 950 pages, $128.

Hyperbaric Medicine Practice is now available in its second edition. This book, extensively revised from the initial 1994 edition, provides a comprehensive summary of an entire medical specialty. Though the intended readership is undoubtedly those who actively practice hyperbaric medicine, it will also serve as a useful reference to those who refer patients for hyperbaric oxygen therapy or have hyperbaric treatment centers within their medical institutions.

In essence, the book represents a primary textbook of hyperbaric medicine. It is divided into 3 sections. Section I (432 pages) provides background to the field. It begins with the history of hyperbaric medicine, tracing its roots back to compressed air therapy in the 19th century. The physics of diving and hyperbaric pressure are next reviewed, along with the physiologic and toxic effects of hyperbaric oxygenation. The remainder of Section I addresses general clinical aspects of hyperbaric oxygen delivery. Individual chapters discuss topics including patient selection, types of hyperbaric chambers, economics of hyperbaric medicine, management of pediatric and critically ill patients, and hyperbaric nursing.

Section II (437 pages) is composed of chapters that individually review the use of hyperbaric oxygen therapy for each of the 13 conditions approved by the Undersea and Hyperbaric Medical Society (UHMS) for treatment. Each provides a review of the physiology of the disease, rationale for use of oxygen therapy, a summary of available animal and/or clinical studies, and treatment protocols. In many instances, didactic case presentations are included. Notably, the chapters are written by authors who are recognized experts in the hyperbaric treatment of the various conditions. In many cases they are individuals who performed pioneering work on particular conditions, in some cases leading to formal UHMS approval for treatment.

Section III (67 pages) contains chapters on 6 conditions not approved by the UHMS for hyperbaric treatment, termed in this book "Investigational Areas." Examples of these include acute myocardial infarction, femoral head necrosis, and ileus. It is to the editors' credit that they clearly distinguish these conditions from those that are approved for treatment, seeking to provide the reader information about nonapproved treatments without endorsing them for therapy. In this regard, it would be appropriate if the chapter on the use of hyperbaric oxygen in the management of fungal disease were moved from Section II to Section III, as hyperbaric treatment of such conditions is generally considered investigational at this time.

Physically, the book is well done. It is well organized and illustrated throughout, including color photographs of various types of hyperbaric chambers on the cover. Figures, tables, and photographs are appropriately included in the text. Referencing is both comprehensive and current for each topic reviewed. The index is adequate but could be improved with better organization and would also be more easily readable if the terms were not italicized.

This book should be considered a basic textbook of hyperbaric medicine and a standard reference for anyone in the field. Undersea and Hyperbaric Medicine was approved by the American Board of Medical Specialties as an official United States medical specialty in 1999. Board certification testing is now offered annually through the American Board of Preventive Medicine. It is a credit to the book that it is included on the approved reading list for that examination. It should be recognized that this book is not the definitive source of information on all the topics included. For those who desire more in-depth information, there are entire books available about many of the individual areas discussed (eg, diving medicine, carbon monoxide poisoning). Nonetheless, a textbook of this type plays an important role for education of those inexperienced in hyperbaric oxygen therapy and as a reference for those with more background.

The other currently available textbook on hyperbaric medicine is the *Handbook on Hyperbaric Medicine* (Oriani G, Marroni A, and Wattel F, editors. Berlin/New York: Springer-Verlag, 1996), which has more European authors and reflects that influence in its approach to the hyperbaric treatment of specific conditions. If one practicing hyperbaric medicine in the United States were to purchase only one of the two books in 2001, I would recommend **Hyperbaric Medicine Practice**, 2nd edition. It is more reasonably priced and has been updated more recently. However, both books would be recommended for the library of anyone active in the delivery of hyperbaric oxygen therapy.

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Hyperbaric Facility Safety: A Practical Guide. Wilbur T Workman, editor. Flagstaff, Arizona: Best Publishing, 1999. Hardcover, illustrated, 754 pages, $128.

There has been a proliferation of clinical hyperbaric facilities in the United States and around the world. Although much has been written about the medical aspects of clinical hyperbaric oxygen therapy, information devoted to the complex issues that comprise hyperbaric facility safety has been limited. These issues include (but are not restricted to) engineering design practices, regulatory guidance, training, staffing, maintenance programs, and operational procedures. Unfortunately, this unparalleled growth of hyperbaric medicine facilities has been without a comprehensive, concise reference addressing the vast and multifaceted topics of hyperbaric facility safety. The development of safety standards historically has been motivated by fatal or catastrophic accidents occurring in pressure vessels. Many existing standards have evolved from operational chamber facilities. The goal of this book is to create a comprehensive source document that can serve as a safety primer and apply to both operational and clinical hyperbaric facilities. The text is organized into 6 sections, with a total of 26 chapters. Several chapters are further subdivided to more clearly present the different international approaches to particular topics as they relate to hyperbaric facility safety.

The first section describes hyperbaric chamber types as classified by the National Fire Protection Agency (NFPA) and the American Society of Mechanical Engineers (ASME). A list of international chamber manufacturers is included. The history of safety standards, including the origination of boiler and pressure vessel laws, is traced, and the regulatory agencies that impact the safety of hyperbaric facilities are introduced. In the United States, the agencies and standards include (but are not limited to) the NFPA, ASME, the ASME Pressure Vessels for Human Occupancy (PVHO) Safety Standards, the American National Standards Institute, the United States Food and Drug Administration, and the Undersea and Hyperbaric Medical Society (UHMS). Standards and regulatory agencies in other countries throughout the world are also described, many of which have adopted United States or European standards, or used them as templates. There are no current regulatory agencies in Latin America, and there are no fire safety standards in several countries/regions in the world. In Germany, members of the Association of German Hyperbaric Centers have established guidelines for quality standards regarding providing uniform treatment procedures, qualifications of staff, and safety precautions for chambers. No truly international safety standard has yet been published. Though it is unrealistic to expect the international hyperbaric community to agree to any one course of action, this book can serve as the definitive reference containing the crucial elements and quality standards to make the choice more informed and less daunting. The text encompasses a detailed portrayal of staffing and training requirements throughout the world, including the organizations that provide the training, certification, and monitoring of continuing education. Education standards and certification requirements throughout the world are diverse, ranging from essentially no standards at all to programs similar in scope to that in the United States. Implicit in the book

is the petition for more universal recommendations for staffing and training programs that are so essential to comprehensive safety considerations. Unfortunately but truthfully, the development of safety standards has in no small way been prompted by the occurrence of tragic chamber mishaps and fatalities. An important and recurrent theme in the text is the need to document and study the mishaps of the past in an attempt to avoid future pitfalls.

The second section describes the subsystems that constitute the hyperbaric facility, including pressurization, piping, breathing gas, electrical, fire suppression, and ventilation. The discussion specifies the hyperbaric codes and standards that directly apply to these facilities, as well as companion codes such as building and potable water.

The third section outlines a concise blueprint for establishing a hyperbaric facility maintenance program, utilizing published recommendations by appropriate agencies, such as the NFPA, ASME, and UHMS, chamber manufacturers' instructions, and equipment operations manuals. The text integrates quality of care considerations with facility safety, appropriately depicting the two elements as fundamental and inseparable.

The fourth section covers fires in the hyperbaric environment. The history of these rare but catastrophic chamber fires is reviewed and serves to accentuate the importance of fire safety considerations. This section discusses in great detail the fire hazards associated with the hyperbaric environment, flammability properties of various substances, and methods of controlling fires, as well as other risk factors in the hyperbaric setting.

The fifth section provides a detailed analysis of factors contributing to accidents, including human error, facility or equipment concerns, and malicious activities. The review of chamber accidents over the past 75 years provides crucial historical information that—if incorporated into a comprehensive hyperbaric incident monitoring program—can be effective in avoiding repeats of these tragedies. The short, separate chapter on Japan's Hyperbaric Mishap Reporting System (Section V, Chapter 5) could probably have been integrated into one of the earlier chapters.

The sixth section offers a practical approach to hyperbaric safety. The first chapter of this section is arguably the most consequential in that an immense amount of information is focused into well-defined elements that constitute an effective facility safety program. This information can then be used as a foundation for (eventual) policies on facility certification. Initial and periodic facility certification is vital to hyperbaric facility safety. Certification standards need to be exhaustive and compulsory to help ensure staff and patient safety and should include periodic evaluation of (both monoplace and multiplace, operational and clinical) hyperbaric facilities for compliance with those standards. Though this book does not directly address the issue of facility certification, the foundation is firmly set for the development and implementation of such a program.

This section also defines and discusses decompression illness as a risk for staff attendants in the multiplace chamber. The critical importance of the interaction and communication between the hospital administration and appropriate regulatory bodies to ensure compliance with safety standards is emphasized. Also discussed are key issues in patient education and recommendations for evaluating clinical chambers in remote locations for safety and appropriateness of care. Analysis of hyperbaric incidents are reviewed, with special attention to prevention and contingency plans. Although contingency plans are vitally important, the text points out that the major focus should be on prevention and the need for hyperbaric facility staff members to have disaster training to practice their responses to urgent or emergency situations. There is a detailed discussion of the Clinical Hyperbaric Evaluation and Testing Program, which is essentially a United States Navy program with UHMS oversight: it provides a template for equipment testing and a ready source of valuable information in the database derived from prior testing.

The intended readership of this book is as diverse as the issues and factors that impact safety in hyperbaric facilities. Certain aspects of the book will be useful to local government officials responsible for enforcement of applicable codes, hospital or facility administrators, facility maintenance staff, quality assurance personnel, and facility safety officers. Other parts of the book will be useful to chamber designers, architects, and equipment manufacturers. Finally, parts of the text will be valuable to physicians, nurses, respiratory therapists, and hyperbaric technicians.

The editor's international approach to hyperbaric facility safety is useful and informative. It offers the opportunity to evaluate programs in other countries and world regions that have hyperbaric facilities, allows for comparisons, and ultimately provides the impetus to combine the best features of each. By design, the editor made little attempt to modify the international authors' chapters. This leads to some redundancy in that the principles of facility safety are much the same worldwide, though standards, practices, and regulatory agencies are quite varied. However, this text illustrates the international commonality in hyperbaric facility safety concerns and is a crucial step toward the development of universal standards.

At present, other than self-certification and verification of the criteria of the ASME PVHO-1 Safety Standard, there are no requirements for a third-party inspection agency or system certification in the United States, and very few countries have such requirements worldwide. It is clear from the text that a comprehensive facility certification program in each country or world region is key to the successful and safe advancement of hyperbaric medicine internationally. The text contains no direct reference to the United States Naval Facilities Engineering Command's certification and maintenance program for hyperbaric facilities. Their model is a superb one to emulate but more comprehensive than necessary for civilian multiplace chambers, since the vast majority of these facilities are not designed with the high levels of complexity and redundancy as the operational naval facilities.

The appearance of the book is entirely professional and is intentionally similar to **Hyperbaric Medicine Practice**, a related textbook also reviewed in this issue. Typographic errors are rare, illustrations are understandable and of high quality, and the text is clear and readable. The information is well researched and applicable, as indicated by the excellent references. The index is indispensable in such a large book that contains an enormous amount of diverse information and will serve as a reference text. Unfortunately, there are a substantial number of index entry page numbers that do not correspond to the text. This will need to be remedied in future editions.

The editor and the contributing authors have done an excellent job of unraveling the complex issues that comprise hyperbaric facility safety. The text reveals the broad range of regulatory agencies and standards,

detailed information about chamber types and subsystems, and a systematic approach to facility preventive maintenance. Focus on prevention of accidents, analysis of past mishaps, involvement of facility administration, staff and patient education, attention to detail, and disaster preparedness drills are all requisite, related components of a comprehensive approach to hyperbaric facility safety. This text has left no stone unturned in the dissection of those factors.

Finally, this book represents an enormous and long overdue effort to create a comprehensive source document that will serve as a safety primer and hyperbaric facility safety benchmark for established and developing hyperbaric programs in the United States and around the world.

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Interstitial Lung Disease, 3rd edition. Marvin I Schwarz MD and Talmadge E King Jr MD. Hamilton, Ontario, Canada: BC Decker. 1998. Hardcover (with CD-ROM), illustrated, 760 pages, $159.

Drs Schwarz and King have been involved with interstitial lung disease (ILD) for many years, and particularly Dr Schwarz has been speaking about it for more years than I care to remember. Previous editions of this book were a prime source for all of us interested in this topic, and this edition continues that distinction.

The approach to the topic taken by the editors in the first chapter of this current edition is to provide principles of approach to the 156 causes of ILD that are referred to in the very first table in Chapter 1! As it turns out, this chapter may be the most useful in the book, as it summarizes etiologic, pathologic, pathophysiologic, clinical, diagnostic, and therapeutic information in concise, clear form. Thus, the reader who uses this source for a general guide or for specific entity identification and clarification will benefit by a careful reading of this opening section.

The following chapter goes into much more detail regarding pathologic anatomy, but sticks with principles that give the reader an overview of both the gross and the microscopic (but particularly the microscopic) morphology of this affliction of the lungs. Drama would have been served by having illustrations in color rather than only in black-and-white, but the price would certainly have been higher as a result, so perhaps the existing compromise is acceptable.

Following is a chapter on abnormal lung function seen in ILD, with emphasis on the physiologic basis of the observed abnormalities—clearly presented and well illustrated, meaning that I, as a nonphysiologist, understood pretty much of what appears in the chapter.

The chapter on imaging techniques repeats the approach of presenting principles first and then dealing with specific entities. The limiting factor in this chapter is the lack of information on ultrasound and scanning techniques that are not dealt with in a general way anywhere in the book—an important omission. Interestingly, magnetic resonance imaging is discussed and its limitations noted, but no opinion is expressed on the other techniques mentioned above. The illustrations of plain chest films, computed tomography, and high-resolution computed tomography are beautiful.

The chapter on pediatric ILD is excellent, but the grim prognosis reflected in many of the diseases described is especially heartbreaking. As an introduction to this specific group of patients, the chapter provides basic information, especially information peculiar to the specific age group.

Chapters 7, 8, 9, and 10 deal with basic biology of inflammation and tissue repair. This is an area that has grown and developed rapidly in the last several years, and the information provided is probably out of date already. But for those of us whose approach to life is clinical, these chapters give an insight into current concepts of the pathogenesis of what we deal with clinically. These facts are a natural lead-in to Chapter 13, which deals with treatment of ILD—not the most satisfying element of this area of medicine!

Two chapters discuss sarcoid: one as an example of immunological events in ILD and the other as a straightforward display of a specific disease causing ILD. I think the appearance of two such chapters is redundant and that the editors should have combined the efforts of Drs Semenzato and Agostini on one hand and those of Drs Stirling, Cullinan, and Dubois on the other. As it is, the latter group has produced what is, in my estimation, the best summary of sarcoid that I have encountered in many years.

Chapter 12, which deals with pulmonary vascular elements of ILD, is brief and repeats information that appears elsewhere, suggesting that more editing could have made this chapter expendable, although there is interesting information presented.

The rest of the book deals with specific entities associated with ILD, and it is in these chapters that I found the greatest variation of usefulness. In some of them there is an emphasis on ILD, how specific disease entity produces ILD, or what is peculiar about ILD as a manifestation of a specific disease. In most of these chapters, however, there are detailed descriptions of the specific diseases, but no special reference to ILD. In other words, this part of the book becomes an incomplete textbook of pulmonary diseases in general rather than a treatise on interstitial diseases in particular. For example, the 3 chapters dealing with industrial lung disease do not specifically deal with ILD, whereas the chapter on drug-induced lung disease emphasizes the interstitial manifestations of these entities. The chapter on pulmonary vasculitis ignores ILD as a unique part of the spectrum, whereas those chapters written by either Dr Schwarz or Dr King are presented from the primary point of view of ILD.

In general, this third edition is well produced, well written, and well indexed. My main reservation concerns the inconsistency of emphasis on ILD noted in the chapters on specific disease entities. I sense that this may be the editors' fault as much as the authors'. If this matter had been dealt with, the book would have been somewhat shorter but just as useful. In general I found the book a rich source of information on the subject of ILD. The book is easy to use as a reference, since the organization is logical and chapter titles are accurate. This book remains the gold standard on this subject for students of ILD, regardless of their level of sophistication

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Skin Signs of Systemic Disease, 3rd edition. Irwin M Braverman MD. Philadelphia: WB Saunders. 1998. Hardcover, illustrated, 682 pages, $152.

Irwin Braverman has always had a specific purpose in the single-author **Skin Signs of Systemic Disease**, and he has kept that purpose in narrow focus in this thoroughly updated third edition of the classic text. It is rare that the title of a medical text so aptly sums up its contents while at the same time omitting from the title what is similarly absent from the discussion on the pages between its covers. This is primarily a book about the art and science of the physical examination, and only the examination of the skin and its appendages at that. It also limits its scope to the cutaneous manifestation of systemic illness, rather than looking at all disorders of the skin. In engaging in precise language, Braverman has tackled the intimidating task of comprehensively detailing the clinical signs and symptoms of all major and many minor systemic disorders. This third edition includes an updated overview of both recent and classic investigational studies and summaries of current understanding of the pathophysiology underlying the cutaneous manifestations he discusses.

In the task he has undertaken the author succeeds spectacularly. By limiting his focus Braverman makes sacrifices when his text is compared with both internal medicine and general dermatology textbooks that aspire to be more comprehensive. These compromises are perhaps necessary to achieve his specific ends. Nevertheless, there is much that a health professional, seeking information and answers to specific clinical problems, will not be able to find if only consulting this book from the shelf. Notably missing is almost any discussion of therapy of either the systemic disorders themselves or the specifics of treating the skin manifestations. Perhaps as a corollary, another weakness is the inconsistent quality of the discussion of the effects of medical treatment in modifying the cutaneous signs of an illness or discussion of them in causing specific cutaneous syndromes. Though the most commonly seen adverse effects of major chemotherapy agents are briefly discussed in the chapter on leukemia, for example, nowhere in the discussion of either pyoderma gangrenosum or Sweet's syndrome (acute febrile neutrophilic dermatosis) is either condition's association with granulocyte colony stimulating factor mentioned. Also absent is all but cursory discussion of the histologic findings and accompanying differential diagnosis that confront the practitioner interpreting the skin biopsy results from a patient with systemic illness.

Providing the expertise that bridges the disciplines of pathology and medicine by understanding the intricacies of interpreting and correlating histologic and clinical findings is one of the greatest strengths that a dermatologic consultation can bring to a patient with systemic illnesses. Unfortunately, this textbook provides little aid to the nondermatologist who wishes to better understand either the strengths or limitations of the diagnostic line on the biopsy reports received from the pathologist. Another particular weakness is expanding on the differential diagnosis of skin findings. For example, granuloma annulare is an idiopathic disorder of the skin that both clinically and histologically must be included in the differential diagnosis of sarcoidosis of the skin. A practitioner unfamiliar with this entity while reading the sarcoidosis chapter might go to the index and thereby through cross-references find that granuloma annulare is associated with diabetes. But it would still take a trip to a more general dermatology reference by the noncognizant for a clear picture of this entity in the differential diagnosis to emerge.

The book is organized into chapters on the major categories of systemic illness described, each with mostly self-contained discussions of specific diseases or syndromes. Each chapter can stand independently of the others. This book also lends itself to being both a quick reference for answering focused questions and a longer, more comprehensive reading of a selected topic. An hour or two carefully reading the sarcoidosis chapter would be well spent by the pulmonary specialist wishing to clarify his or her thinking about various cutaneous clues that can help diagnose this entity prior to the chest radiograph. Just as feasible is a quick reference to the hypersensitivity syndromes chapter to help distinguish erythema multiforme from erythema chronica migrans for the intensive care specialist trying to sort out an annular rash in an intensive care unit patient.

Skin Signs of Systemic Disease is not a beginner's textbook. Unlike either general dermatology texts or manuals of physical examination, there are no preface chapters or even a glossary to explain to the nondermatologically savvy the difference between macule and patches, vesicles and bullae or papules and nodules. This is somewhat compensated by the author's gifted writing ability. Few authors I have read are equally able to evoke a clinical picture with both careful and judicious descriptive language. This is helpful, because the pictures in the text are good but not spectacular. Small (one sixth of the page on average) and black-and-white, the photographs are well chosen to represent both classic and less usual manifestations of the conditions described. There are color plates of, again, small photographs that are interspersed between pages of the text, but these are often several pages out of context and thus less directly linked to the topic being discussed. Dermatology texts with full color photographs throughout can be a visual feast, however, because of the cost of color printing, extensive color illustrations also make a text about skin disease 3–4 times as expensive as a similar text in another subject. For a dermatology text, this one is more affordable than most, listing between $145 and $155 at an online bookseller.

The clinician with a systemically ill patient without a known diagnosis will find this book frustrating in terms of differential diagnosis. In what is probably a response to similar criticism, the author has added, in the preface, small tables focusing on differential diagnosis. This afterthought, however, lacks the attention to detail and logical and comprehensive explanations that characterize the rest of the text. Without the usual rich commentary by the author that is found in the body of the work, this tabular discussion of differential diagnosis will probably leave the reader unsatisfied.

Understanding the narrow focus and the author's specific intent, however, the reader who is only after a discussion of the cutaneous aspects of internal medicine (and some pediatrics) will find that Braverman rather spectacularly succeeds at accomplishing his task. For a summary of both the classic understanding and current science of skin findings in systemic disease, careful sifting through dozens of review articles from major and minor journals is unlikely to find substantially more comprehensive treatments. That same search of review articles is even less likely to find anything more comprehensive, for this author is an excellent writer. Braverman is able to be factual while at the same time bringing enough opin-

ion and personal observation to his commentary to make for rich and captivating reading. This edition is as thoroughly updated and referenced as any article in a specialty journal, yet at the same time there is character and personality in the language that is best found in a well written single-author text such as this.

In this day and age of advanced MEDLINE searches and quick and easy photocopying of articles from journals in library stacks, the incentive to reach for one's own shelf for medical information seems to be less and less by the year. First know that this text is not a comprehensive general dermatology text, that within the book the words paint a better picture than the photographs, that it gives minimal discussion or guide to therapeutics, and that those without basic knowledge of the language of dermatology will find little help. However, if on your shelf, **Skin Signs of Systemic Disease** will reliably provide a well written, thorough, and thoughtful up-to-date discussion of the clinical manifestations and pathophysiologic bases of major and, most importantly, minor systemic diseases. With it at your fingertips, that MEDLINE search and trip to the library will probably be unnecessary.

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MD Consult
(reviewed December 26, 2000)

MD Consult (http://www.mdconsult.com) is an online reference tool available only through the World Wide Web. It was developed as a joint venture by 3 leading medical publishers (WB Saunders, Mosby, and Lippincott, Williams & Wilkins) to provide a single uniform access to all areas of clinical information needed by a physician in the course of patient care. The focus is on the practicing physician, although it can be a valuable resource for other health care providers as well.

There are subscription models to fit most situations. The personal subscription ($199.95/year or 19.95/month) allows the user to customize the update function to deliver clinical news of interest or to e-mail Food and Drug Administration approval news, or safety alerts. There are also group and institution-wide subscriptions, with individual customization available. The pricing for those subscriptions is available on request.

MD Consult is divided into two general portions: "updates" and "answers."

"Updates" contains news likely to be of interest to a clinician: current health and medical news plus drug alerts and Food and Drug Administration approvals. "Today in Medicine" is the last 7 days from Reuters Health, broken down to general interest and specialty areas. In "This Week's Journal," the tables of contents plus abstracts for the most current issue of *Journal of the American Medical Association*, *The Lancet*, *British Medical Journal*, *Annals of Internal Medicine*, and *New England Journal of Medicine* are provided for current awareness.

"Answers" is a gateway to a wealth of information, much of it available in full text, searchable in a single search screen. The user can either search all of **MD Consult** or limit the search to 38 reference books in all areas of internal medicine, 500 practice guidelines, drug information from Mosby GenRx, patient education materials, or MEDLINE.

The Reference Books section includes many well-known titles, such as Bone's *Pulmonary and Critical Care Medicine*, Miller's *Anesthesia*, and Mandell's *Principles and Practice of Infectious Diseases*. The textbooks can also be used traditionally, going from the table of contents to a chapter. The full-text journals and the year books must be accessed through the search form.

The best approach is to search using the key elements of your question: for example, the phrase "respiratory therapy for COPD" (chronic obstructive pulmonary disease) retrieved 121 items: 2 references from the reference books and 119 from the journal literature.

Sorted by relevance, there were 64 articles from journals such as *Chest*, *Critical Care Medicine*, *Immunology and Allergy Clinics of North America*, and *Clinics in Chest Medicine*. There were also 2 full-text commentaries from the year books. The remaining 55 were articles with summaries from MEDLINE, 1966 to present.

A slightly different search, for respiratory therapy for children with asthma, yielded 1 reference text, 1 practice guideline, and 61 articles, 33 of which were available in full text.

There is also a feature called "Find More Articles Like This" that allows you to search further using an example of an article already found.

This type of access is both a strength and a weakness. An answer can be searched for quickly across the full range of content, or just in textbooks, or just in journal literature. The search query box is straightforward, with blanks to fill in. But the search must be "translated" from a sentence question such as "what type or respiratory therapy is effective in COPD" into "respiratory therapy" and "COPD or chronic obstructive pulmonary disease." It becomes very cumbersome if the question is complex. The biggest weakness is that journal articles can be located only by a search. There is no mechanism to go directly to a known article in *Chest* or *Critical Care Clinics*, or to browse the table of contents of the most current issue.

Once found, an article or chapter can be displayed or printed one item at a time. There is no mechanism to save or e-mail the results. Access to the journal literature is through a current search only. There is no capability of saving a search to run each month, nor of e-mailing updates as new material is added. In fact, current issues are not immediately available.

MD Consult announced in December 2000 that a new product focused on cardiology will debut in 2001. Other specialty areas are being planned. The focus continues to be on the general practitioner or family physician. The specialty products will require separate subscription.

Stat-Ref! Plus is a similar reference product. Made by Teton Data Systems, *Stat-Ref! Plus* is accessible on CD-ROM or via the World Wide Web (at http://www.statref.com). Many of the same textbooks are available via *Stat-Ref! Plus*, as well as the *Current Diagnosis and Treatment* specialty series and the *Medical Letter on Drug Therapeutics*. However, *Stat-Ref! Plus* does not include full-text journals or MEDLINE.

For a small clinic or a respiratory therapist in a small hospital at a distance from a library, **MD Consult** could be very useful. Though not replacing standard reference texts such as Burton's *Respiratory Care: A Guide to Clinical Practice* or professional journals, in a setting where a broader range of problems are common, access to **MD Consult** could substitute for general references or reliance on memory in the absence of a library. The drug information and textbooks provide more depth than searching PubMed or Medscape for access to free full-text journals. Searching **MD Consult** is easy and quick, but the cost per day for a personal (monthly) subscription is $1.00, plus the cost of an Internet connection. Actual probable use should be carefully balanced against the benefits.

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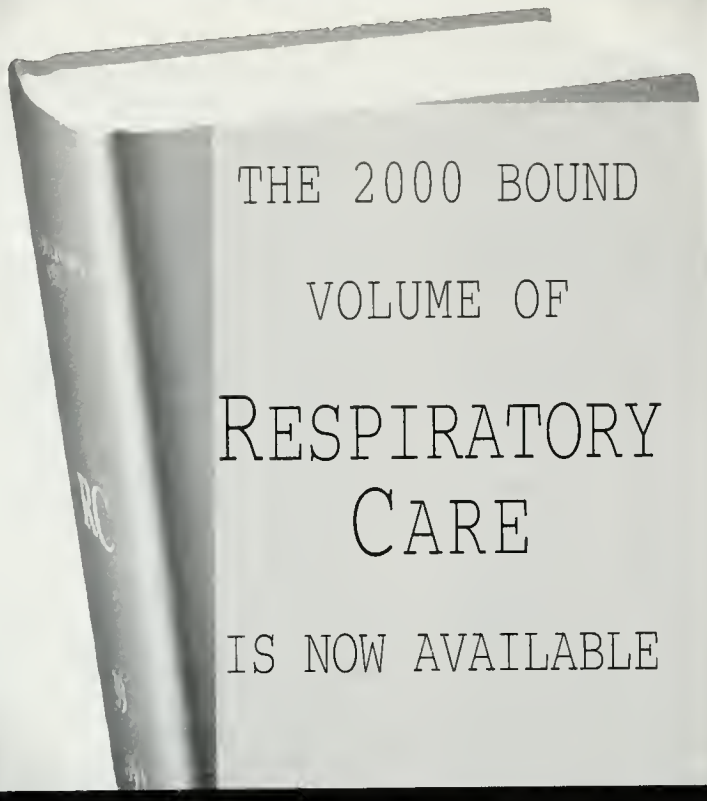

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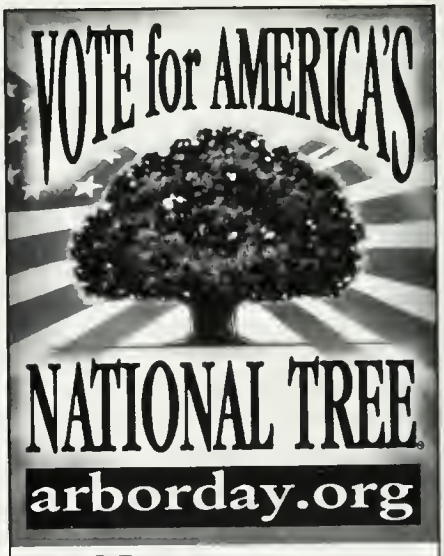

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An abstract may report **(1) an original study, (2) the evaluation of a method, device or protocol, or (3) a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, or health care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract will be the only evidence by which the reviewers can decide whether the author should be invited to present a poster at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions*. Give specific information. Do not write such general statements as "Results will be presented" or "Significance will be discussed."

ESSENTIAL CONTENT ELEMENTS

Original study. Abstract *must* include (1) Background: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results.

Method, device, or protocal valuation. Abstract *must* include (1) Background: identification of the method, device, or protocol and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience or a lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate.

Case report. Abstract *must* report a case that is uncommon or of exceptional educational value and must include (1) Introduction: relevant basic information important to understanding the case, (2) Case Summary: patient data and response, details of interventions, (3) Discussion: content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

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- ☐ Master's Degree
- ☐ Doctorate Degree

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- ☐ 0-2 years
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- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

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I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

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Corporate author journal article:
American Association for Respiratory Care. Clinical Practice Guideline. Removal of the endotracheal tube. Respir Care 1999;44(1):85-90.

Article in journal supplement: (Journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval.)
Barnes PJ. Endogenous inhibitory mechanisms in asthma. Am J Respir Crit Care Med 2000; 161(3 Pt 2):S176-S181.

Abstract in journal: (Abstracts citations are to be avoided, and those more than 3 years old should not be cited.)
Volsko TA, De Fiore J, Chatburn RL. Acapella vs flutter: performance comparison (abstract). Respir Care 2000;45(8):991.

Editorial in a journal:
Giordano SP. What's that sound? (editorial) Respir Care 2000;45(10):1167-1168.

Editorial with no author given:
The perils of paediatric research (editorial). Lancet 1999;353(9154):685.

Letter in journal:
Piper SD. Testing conditions for nebulizers (letter). Respir Care 2000;45(8):971.

Book: (For any book, specific pages should be cited whenever reference is made to specific statements or other content.)
Cairo JM, Pilbeam SP. Mosby's respiratory care equipment, 6th ed. St Louis: Mosby; 1999:76-85.

Corporate author book:
American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Chapter in book with editor(s):
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American Lung Association. Trends in pneumonia, influenza, and acute respiratory conditions mortality and morbidity. February, 2000. http://www.lungusa.org/data. Accessed November 20, 2000.

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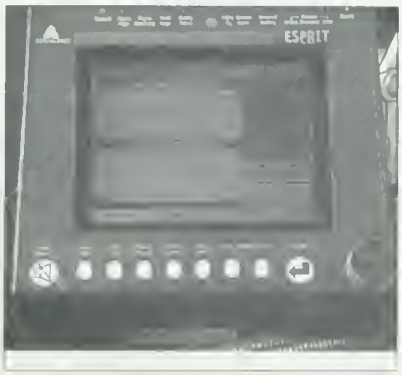

Color Screen Option for Ventilator. Respironics has released a new color screen option for its Esprit® ventilator. Company press materials say the new screen is designed to enhance a clinician's ability to identify displays and facilitate the unit's graphical user interface. Respironics says the screen uses color to draw immediate attention to ventilator status, setting changes, and alarms, and that it can be included with initial ventilator purchase or added later. For more information from Respironics, circle number 199 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Portable Metabolic Unit. SensorMedics has introduced the VmaxST, a portable metabolic unit the company calls exciting new technology for medical, research, and fitness professionals who assess oxygen consumption. According to the company, this new device allows subjects to be tested outside the laboratory where they actually perform daily exercise routines like walking, climbing, biking, skating, rowing, or even mountain climbing. Company press materials describe the unit as weighing less than any similar product on the market, and offering bi-directional telemetry that lets you view data up to 1,000 meters away and communicate with the exerciser. SensorMedics says the VmaxST is also convenient to use in the lab, interfacing with many ergometers and treadmills and providing downloadable data stored directly in the unit. For more information from SensorMedics, circle number 200 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Updated Ventilator Series. Pulmonetic Systems has added several new features to its series of LTV™ ventilators. According to the company, the LTV1000 now offers inspiratory/expiratory hold. Pulmonetic representatives say this new feature allows for patient diagnostic monitoring which aids in the assessment of therapeutic decision. The company also says monitor scroll has been added to its LTV series allowing data to scroll automatically and continuously provide critical patient information. For more information from Pulmonetic Systems, circle number 201 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

ISE Electrodes. ALKO Diagnostic Corporation has recently developed ISE electrodes for AVL 9100 series analyzers. According to the company they now offer the Na+, K+, reference electrodes and reference housing for use on the AVL 9120, 9130, 9140, & 9180. ALKO says its products are designed for use in place of original equipment manufacturer's consumables. Correlation data are available upon request to ALKO. For more information from ALKO Diagnostic Corporation, circle number 202 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Pulse Oximeter. Datex-Ohmeda Inc, Ohmeda Medical, and Masimo Corporation have joined together to distribute Masimo's new Radical™ Signal Extraction pulse oximeter. Datex-Ohmeda press materials describe the Radical pulse oximeter as the first end-user product developed by Masimo that uses the company's Signal Extraction Technology (SET). The company says SET is a method for measuring signals accurately and reliably in the presence of patient motion and low perfusion. According to Datex-Ohmeda, the device can be used as a bedside monitor, a handheld oximeter, or can upgrade existing multi-parameter monitors to Masimo SET through its SatShare™ interface. For more information from Datex-Ohmeda Inc, Ohmeda Medical, circle number 203 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

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Calendar of Events

Date	AARC & Affiliates Programs	Contact
April 4–5	USRC 2001 Conference; **Ogden, UT**	Utah Society for Respiratory Care, peberele@weber.edu
April 9–11	North Dakota Society for Respiratory Care's Annual Educational Symposium; **Fargo, ND**	Michelle Sele, (701) 234-6777, michellesele@meritcare.com, www.ndsu.nodak.edu/ndsrc
April 12–13	Rhode Island Society for Respiratory Care's 17th Annual Conference, **Newport, RI**	Wayne P. Foresti, (401) 769-8758, RIWPF732@aol.com
April 19–20	PSRC 4th Annual Eastern Regional Conference and Exhibition, **King of Prussia, PA**	Pennsylvania Society for Respiratory Care, Ann Cusano, (215) 646-7300, ext. 428, cusano.a@gmc.edu
April 25–27	Region II 28th Annual Meeting; **Covington, KY**	Jeff Jones, (800) 691-3041, #1, www.bright.net/~dsibb/reg2rc.htm
May 9–10	Maine Society for Respiratory Care's Spring Fling; **Lewiston, ME**	Roberta Crockett, (207) 262-2214
May 11	ASRC Diamond Conference, **North Little Rock, AR**	Arkansas Children's Hospital, UA Medical Sciences, Kesha Mack, (501) 661-7962, mackkeshav@exchange.uams.edu
June 6–8	FSRC State Convention; **Fort Lauderdale, FL**	Pat Nolan, (561) 546-1863, (800) 447-3772, fsrc@inetw.net
June 13–15	Illinois Society for Respiratory Care's 33rd Annual Convention; **Oak Brook Terrace, IL**	Kelli DeBerry, (847) 981-3581, www.isrc.org
July 21–23	Management and Education Sections, Summer Forum; **Naples, FL**	AARC, (972) 243-2272, clay@aarc.org
July 23–24	Asthma Disease Management Seminar, **Naples, FL**	AARC, (972) 243-2272, clay@aarc.org
Sept. 26–27	MSRC Annual Meeting, **Sturbridge, MA**	Valeri-Ann Bolduc, (508) 429-7478, O2val@aol.com
Dec. 1–4	47th International Respiratory Congress; **San Antonio, TX**	AARC, (972) 243-2272, clay@aarc.org

Date	Other Meetings	Contact
May 12–14	Spring Sleep Seminar 2001, **Branson, MO**	Bill Rivers or Melinda Trimble, (501) 713-1272
Oct. 2–4	Cardiorespiratory Diagnostics 2001; **Las Vegas, NV**	Medical Graphics Corporation, Mari Orke, (800) 950-5597, ext. 444, www.medgraph.com

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 90 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc.). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept., 11030 Ables Lane, Dallas TX 75229-4593.

Scheduled Professor's Rounds 2001

Program #1 Taking the Mystery Out of Ventilator Weaning for Children—Peter Betit BS RRT FAARC; Host Richard D Branson BA RRT FAARC—Video March 13 Audio April 10

Program #2 Pulmonary Rehabilitation: Standard Care for Chronic Lung Disease Patients—Trina Limberg BS RRT; Host Thomas J Kallstrom RRT FAARC—Video March 27 Audio April 17

Program #3 Noninvasive Ventilation: The Latest Word—Dean R Hess PhD RRT FAARC; Host Richard D Branson BA RRT FAARC—Video April 24 Audio May 29

Program #4 Patient Education for the Asthmatic—Tracey Mitchell RRT; Host Thomas J Kallstrom RRT FAARC—Video May 22 Audio June 19

Program #5 ARDS: The Disease and Its Management—Leonard D Hudson MD; Host David J Pierson MD FAARC—Video June 26 Audio July 17

Program #6 New Respiratory Drugs: What, When, and How—Joseph L Rau PhD RRT FAARC; Host Patrick J Dunne MEd RRT FAARC—Video August 14 Audio September 11

Program #7 Invasive Ventilation: The Latest Word—Richard H Kallet MS RRT; Host Richard D Branson BA RRT FAARC—Video September 25 Audio October 16

Program #8 Test Your Lungs-Know Your Numbers-Prevent Emphysema—Thomas L Petty MD FAARC; Host David J Pierson MD FAARC—Video October 23 Audio November 20

Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
- Current job listings
- American Respiratory Care Foundation fellowships, grants, & awards
- Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
- Subject and Author Indexes
- Contact the editorial staff
- OPEN FORUM; submit your abstract online

Asthma Management Model System
http://www.nhlbi.nih.gov

Keys to Professional Excellence
http://www.aarc.org/keys/

Committee on Accreditation for Respiratory Care
http://www.coarc.com

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For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, or e-mail: nbrc-info@nbrc.org

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Dräger Medical	Evita Series Vents	119	800-437-2437	C2
Hans Rudolph Inc	Research Pneumotach System	120	800-456-6695	305
Ingmar Medical	Lung Simulator	140	800-583-9910	311
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Kaiser Permanente	Recruitment	124	800-331-3976	325
Mallinckrodt	Ventilators	110	800-635-5267	C3
Praxair Inc	Portable Medical Oxygen Unit	122	800-299-7977	300
ResMed	Ultra Mirage Mask	117	800-424-0737	302
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